



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 56

Alan R. Katritzky

Advances in

Heterocyclic Chemistry

Volume 56

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Advances in

HETEROCYCLIC CHEMISTRY

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ACADEMIC PRESS, INC.

Harcourt Brace Jovanovich, Publishers

San Diego New York Boston

London Sydney Tokyo Toronto

Volume 56

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Academic Press, Inc.

1250 Sixth Avenue, San Diego, California 92101-4311

United Kingdom Edition published by

Academic Press Limited

24-28 Oval Road, London NW1 7DX

Library of Congress Catalog Number: 62-13037

International Standard Book Number: 0-12-020756-7

PRINTED IN THE UNITED STATES OF AMERICA

93 94 95 96 97 98 QW 9 8 7 6 5 4 3 2 1

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Preface

Volume 56 of *Advances in Heterocyclic Chemistry* consists of four chapters. Drs. Douglas Lloyd and Hamish McNab from Scotland have provided an updated account of the chemistry of 2,3-dihydro-1,4-diazepines, a subject which has not been specifically reviewed for eighteen years and one with which these authors have been intimately concerned.

Professor Nicolò Vivona and his colleagues from Palermo, Italy, have provided an overview of the present state of ring transformations of five-membered heterocycles which brings up-to-date a previous account by the same group published nearly 20 years ago in Volume 29 of these *Advances*.

Dr. Gordon Rewcastle of the University of Auckland, New Zealand, and your Editor have covered the chemistry of sp^2 -carbanions as generated in the vicinity of heterocyclic nitrogen atoms, a field that has expanded immensely in the last several years.

Finally, the concept of aromaticity in heterocyclic chemistry is the subject of an overview by Professor V. I. Minkin and Drs. B. Ya. Simkin and M. N. Glukhovtsev of Rostov State University in Russia. This new review shows just how wide the aromaticity concept has become. The present authors have successfully extended its range to the consideration of numerous very diverse heterocyclic systems.

ALAN R. KATRITZKY

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2,3-Dihydro-1,4-diazepines and 2,3-Dihydro-1,4-diazepinium Salts

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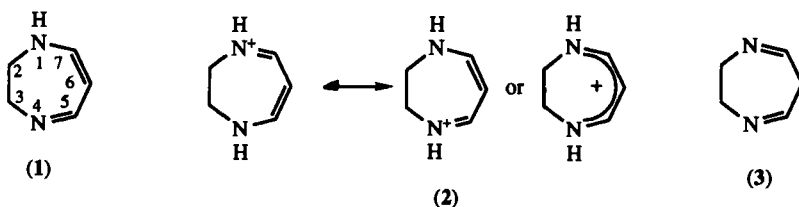
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I. Introduction

Diazepines in general were reviewed in *Advances in Heterocyclic Chemistry* in 1967 (67AHC21), and a review specifically concerned with 2,3-dihydro-1,4-diazepines was published in 1974 (74AHC1). Shorter updating reviews on the latter diazepines have appeared (78H549; 79MI1), but it seems appropriate to provide an up-to-date overall review.

The first example of a 2,3-dihydro-1,4-diazepine was prepared in 1940 (40HCA1139), although a reaction product had been described earlier as a diazepine (15MI1), but is now known to be an acyclic compound. In recent years their chemistry has been studied extensively. One major source of interest was the resemblance between the chemistry of 2,3-dihydro-1,4-diazepinium salts and that of benzenoid compounds in the manner in which both underwent electrophilic substitution reactions, this despite the positive charge carried by these salts [64CI(L)1760; 71MI1; 72AG447, 72AG(E)404]. This reactivity is associated with the presence of a *vinamidinium* (1,5-diazapentadienium) system within the molecules [76AG496, 76AG(E)459].

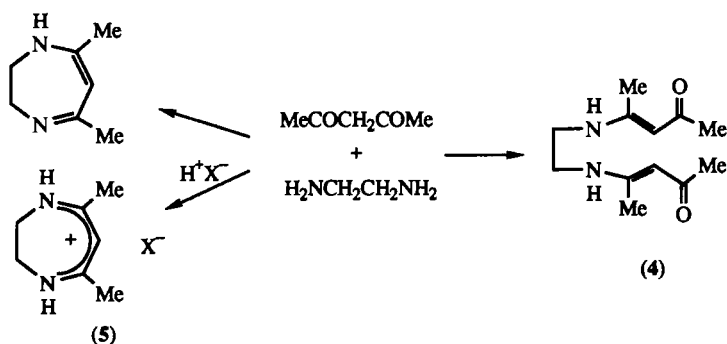
Throughout this article, the terms "dihydrodiazepine" and "dihydrodiazepinium" are used exclusively to refer to 2,3-dihydro-1,4-diazepines (1) and their monocations (2), respectively. Spectroscopic data show that the dihydrodiazepines normally exist in the conjugated form (1) rather than in the tautomeric bisimino form (3).



II. Preparation of Dihydrodiazepines and Dihydrodiazepinium Salts

The first dihydrodiazepine and dihydrodiazepinium salt to be prepared, the 5,7-dimethyl derivatives, were obtained by condensation of acetylacetone with ethylenediamine (40HCA1139), and the reaction between 1,3-dicarbonyl compounds and 1,2-diamines has remained the commonest method for the preparation of these compounds.

The original workers had shown that under different conditions an alternative product, the bisoxoenamine 4, was formed (40HCA1139).



A detailed examination of the reactions between acetylacetone and *trans*-1,2 diaminocyclopentane in aqueous solution (56JCS2597) showed that at room temperature a bisoxoenamine is the major product in neutral and mildly alkaline conditions, whereas the dihydrodiazepine (or its salt) is the sole product at pH values less than 6 or greater than 10. The results derive from the facts that dihydrodiazepines or their salts are extremely stable compounds over a very wide range of pH and their hydrolysis may be ignored save at high alkalinity, whereas the bisoxoenamines are readily hydrolyzed. At all but moderately alkaline pH the latter hydrolysis equilibrium is such that this condensation is effectively suppressed, leaving formation of the dihydrodiazepine to proceed without competition. At moderately alkaline pH, however, not only is the bisoxoenamine stable, but in addition it precipitates out of solution. Thus its formation competes successfully with dihydrodiazepine formation, and it is the predominant product. At higher temperatures the bisoxoenamine does not precipitate out and hence the reaction equilibria no longer favor its formation and yields of bisoxoenamine drop sharply, even at the most favored pH values (56JCS2597). Very similar results have been found in reactions of other alicyclic or aliphatic diamines with acetylacetone (UP1).

Hexafluoroacetylacetone reacts with ethylenediamine to give a bisoxoenamine, which, when recrystallized, sublimed, or just kept, is transmuted into the 5,7-bis(trifluoromethyl) dihydrodiazepine (70MI1).

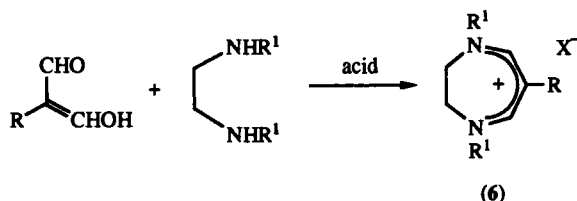
Dihydrodiazepinium salts are commonly obtained by heating the reactants in acetic acid followed by addition of perchloric acid to precipitate the perchlorate salt; alternatively potassium hydroxide may be added to precipitate the dihydrodiazepine base [66JCS(C)780]. A range of dihydrodiazepines or their salts has been prepared in this general way [40HCA1139; 56JCS2597; 66JCS(C)780; 67JCS(C)2340; 68JCS(B)1536; 69JCS(C)1081; 75JHC611; 76IJC(B)1004; 86MI1], including the highly substituted 5,7-diethyl-2,2,3,3-tetramethyl derivative (89LA133).

Sometimes slight variations in the conditions result in improved yields for individual dihydrodiazepines [68JCS(B)1536]. In particular, when aryl diketones are used as reactants, somewhat different reaction conditions may be required [67JCS(C)2340; 69JCS(C)1081]. Thus in the reaction of benzoylacetone with ethylenediamine, a bisoxoename is the main product over a much wider pH range, whereas in alkaline solution yet another product is formed, the bisimine derived from ethylenediamine and acetophenone, resulting from hydrolytic cleavage of either the ketone or the bisoxoename [67JCS(C)2340]. Amended conditions are thus required to obtain the best yields of dihydrodiazepine in this case [67JCS(C)2340] and also from other aryl diketones [69JCS(C)1081] where differences arise because of the lower reactivities of aryl-substituted carbonyl groups.

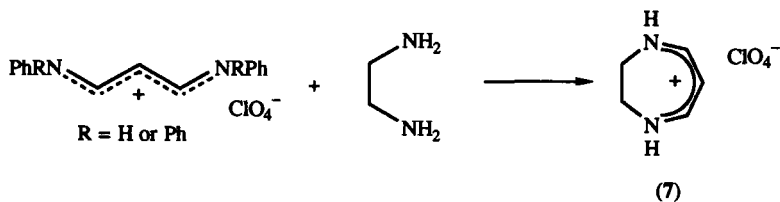
An alternative method for the preparation of the dihydrodiazepinium salt **5** involves the reaction of ethylenediamine dihydrochloride with acetylacetone [67JCS(C)2400]. Dihydrodiazepines have also been obtained from reactions between diketones and ethylenediamine (free base) in ethanol (71MI1; 78JIC577; 78MI1).

Dihydrodiazepinium salts can also be prepared by the reaction of 1,3-diketones with *N*-alkylethylenediamines [69JCS(C)1081; 75JHC611], *N,N'*-dialkylethylenediamines [68JCS(B)1536; 69JCS(C)1081], or *N,N'*-diarylethylenediamines [66JCS(C)93]. When both the diamine and the dicarbonyl compounds involved are unsymmetric, two isomeric dihydrodiazepinium salts may be obtained; thus, for example, *N*-methylethylenediamine and benzoylacetone give a mixture of 1,5-dimethyl-7-phenyl and 1,7-dimethyl-5-phenyl derivatives [69JCS(C)1081]. A dihydrodiazepine has also been made from a 3-ketoaldehyde and ethylenediamine [68JCS(B)1536].

Malonaldehyde, formed *in situ* from a tetra-alkylacetal, or substituted malonaldehydes or their tetraacetals react with ethylenediamine [66JCS(C)93; 68JCS(B)1536; 71LA207; 75HCA2283; 77CCC3455; 78CCC1248; 82ZN(B)1187; 86LA1368; 88CCC1529] or its *N,N*-dialkyl [66JCS(C)93; 68JCS(B)1536; 77CCC3455; 78CCC1248] or *N,N*-diaryl [60CB264; 66JCS(C)93; 75LA470; 84LA649; 85LA1969; 86LA1368] derivatives to provide 6-substituted dihydrodiazepinium salts.



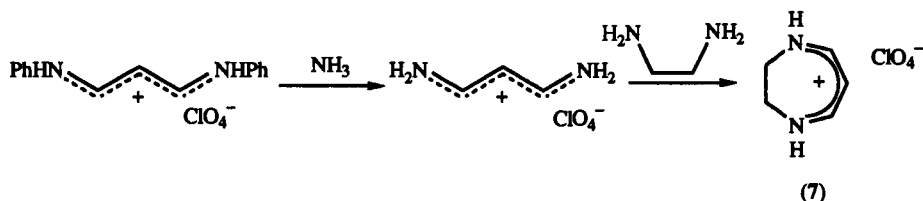
The unsubstituted salt (**6**, $R=R^1=H$) is obtained in this way only in low yield. A much better method is available in the reaction of a salt of the bisanil, or better the bis(*N*-phenylanil) of malonaldehyde with ethylenediamine (73S791).



1,4-Dimethyldihydrodiazepinium perchlorate was made similarly from a salt of the bis (*N*-methylanil) of malonaldehyde and *N,N*¹-dimethylethylenediamine [65AG545; 65AG(E)525].

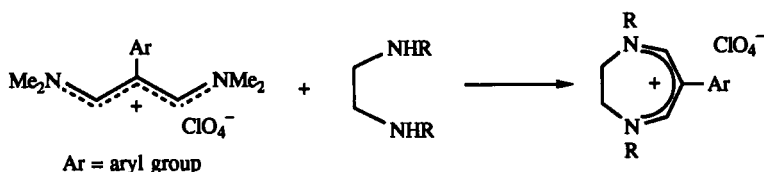
The bisanils are examples of 1,5-diazapentadienium or vinamidinium salts, and these have found wide use as precursors of dihydrodiazepinium salts [77TL2709; 78JCS(P1)1453; 81JCR(S)356; 81JCS(P1)726; 86LA1368]. The reactions between diamines and dicarbonyl compounds are commonly unsuitable for the preparation of 5,7-unsubstituted dihydrodiazepinium salts, as in the case quoted above for the preparation of **7**, because the latter undergo solvolysis under the conditions that thermodynamically favor their formation [78JCS(P1)1453]. When vinamidinium salts are used instead of dicarbonyl compounds, neutral conditions are maintained and hence solvolysis of the product is no longer a problem. When *N,N*¹-diphenylvinamidinium salts are used, as in the preparation of **7**, high dilution conditions are required to obtain good yields [78JCS(P1)1453]. This is a result of there being a considerable difference in the rates of displacement of the two arylamino groups, which causes polymerization rather than cyclization to be kinetically favored in solutions of normal concentration (78JCS(P1)1453). The driving force for the formation of dihydrodiazepinium salts is thermodynamic, and takes advantage of the good leaving tendencies of arylamines. An alternative physical driving force can be provided in such reactions by utilizing the selective removal of a volatile amine, which can be boiled out of the reaction mixture. This approach was applied by first passing ammonia through a solution of a dianil salt, which led to the formation of an unsubstituted vinamidinium salt.

Reaction of the heated solution of this salt with ethylenediamine gives the parent dihydrodiazepinium cation in high yield without recourse to high dilution techniques and provides the most convenient method for its



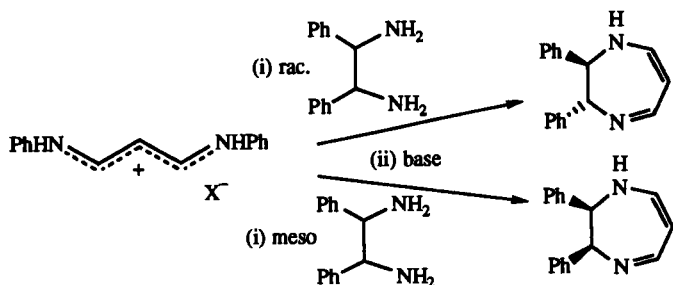
preparation [78JCS(P1)1453]. The method has been used to prepare a variety of other dihydrodiazepinium salts, including some hitherto unobtainable by other ways [78JCS(P1)1453; 81JCR(S)356; 81JCS(P1)726].

An alternative modification uses *N,N,N',N'*-tetramethylvinamidinium salts as starting materials.

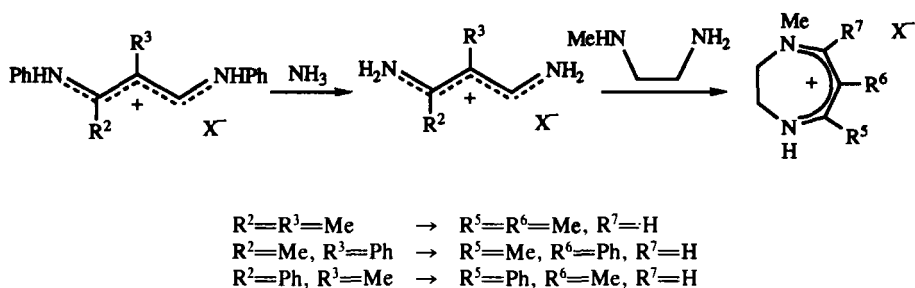


In ring-formation a volatile amine (NHMe_2) is again displaced and may be boiled out of the reaction mixture. This method has proved useful for the preparation of various 6-aryldihydrodiazepinium salts [81JCS(P1)726; 86LA1368]. It proved impossible, however, to prepare 1,4,6-triaryldihydrodiazepinium salts from vinamidinium salts, even using the ammonia method; these have been made from the sodium salt of the appropriate arylmalonaldehyde [81JCS(P1)726].

Racemic and *meso* 2,3-diphenyldihydrodiazepines have been prepared starting from racemic and *meso* 1,2-diamino-1,2-diphenylethane (77TL2709).

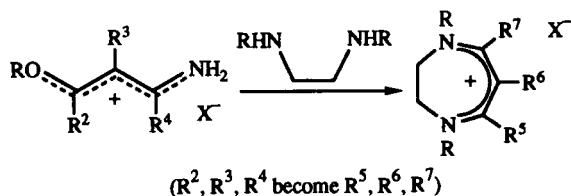


Regiospecific reactions occur between unsymmetric diamines and unsymmetric vinamidinium salts [81JCR(S)356; 81JCS(P1)726].



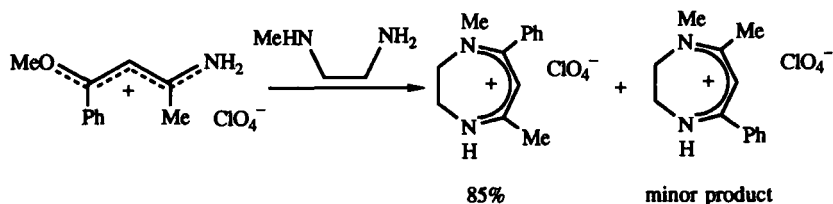
These results are truly regiospecific; in each case only one of the two possible alternative products is formed. In each case, the more reactive ends of the two ambident reagents have reacted with one another and, in doing so, have also produced the less crowded and thermodynamically more stable product [81JCR(S)356].

In addition to vinamidinium salts, 5-aza-1-oxapentadienium salts, themselves obtained by alkylation of oxoenamines, also react rapidly with 1,2-diamines under mild neutral conditions to give good yields of dihydrodiazepinium salts [78JCS(P1)1453].



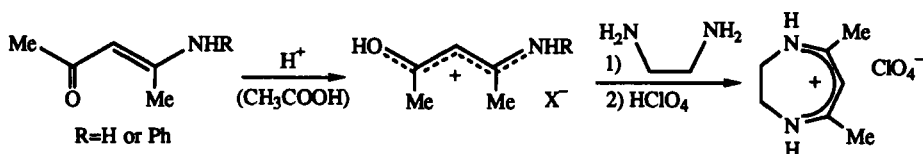
Since the azaoxapentadienium salts are intrinsically unsymmetric, in reaction with unsymmetric diamines two different products are possible.

The alkoxy group is the better leaving group and the more nucleophilic amino group attacks preferentially at that site, for example [78JCS(P1)1453].

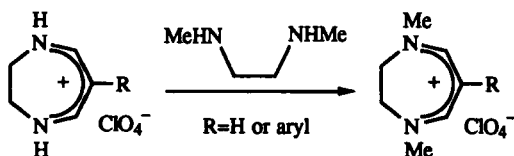


When benzoylacetone reacts with *N*-methylethylenediamine, the other isomer is the major product (78%) [69JCS(C)1081], so that alternative regioselectivity is possible by suitable choice of reactant.

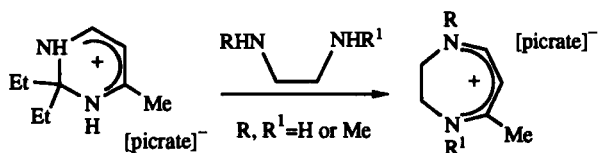
Dihydrodiazepinium salts can also be prepared from oxoenamines in acid solution [78JCS(P1)1453; 86LA1368]; reactions presumably proceed via formation of an azaoxapentadienium salt. Dihydrodiazepinium salts



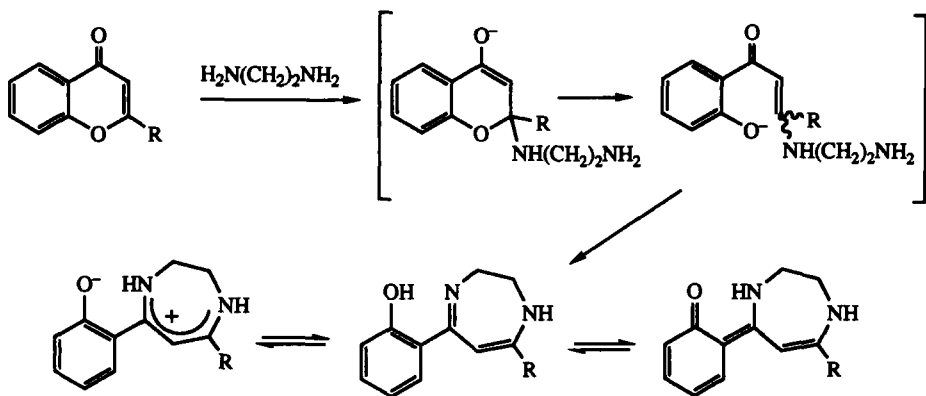
are themselves vinamidinium salts and might undergo reaction with 1,2-diamines to provide other dihydrodiazepinium salts:



The reactions shown do proceed [75JCS(P1)1260; 81JCS(P1)726] but the reaction is not of general application; for example, the reverse of the above reaction does not take place. Steric factors commonly seem to interfere. 1,2-Dihydropyrimidininium salts, which also incorporate a vinamidinium system in their structure, likewise can react with 1,2-diamines to give dihydrodiazepinium salts [76JCS(P1)1784], e.g.

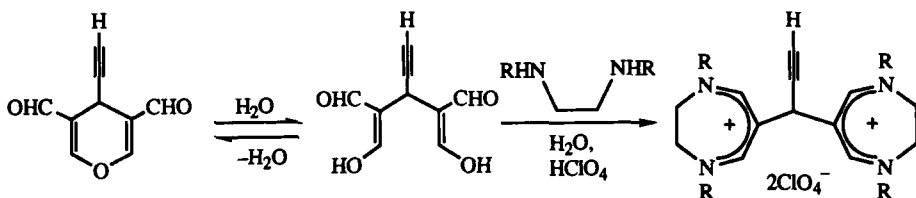


Chromones react with ethylenediamine to give dihydrodiazepines (71KGS17; 82MI1; 82MI2; 85S339; 87MI1). This presumably involves the customary attack of an amine at the 2-position of the chromone, which leads to formation of an oxoenamine that can cyclize to give the dihydrodiazepine.

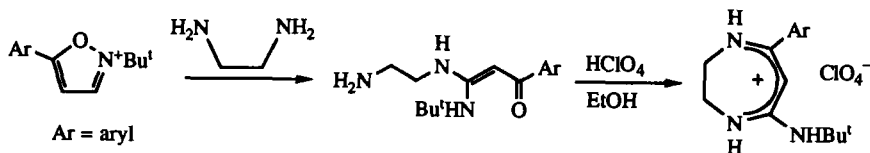


There are three possible alternative tautomeric forms of the product (85S339). A similar reaction takes place with iminium derivatives of chromones (85S339).

Bisdihydrodiazepinium salts have been obtained from reactions of ethylenediamines with a 4*H*-pyrindialdehyde; the latter in aqueous solution is an equilibrium with a bismalonaldehyde (77M929).



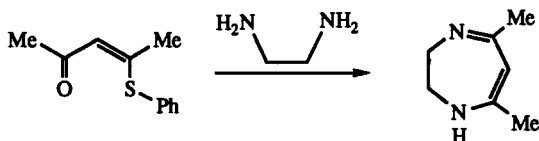
5-Aminodihydrodiazepinium salts have been prepared by the reaction of ethylenediamine with oxazolium salts (76GP2512510).



A dihydrodiazepine has been obtained by a substitution/condensation reaction from a phenylthioenone (85JHC405)

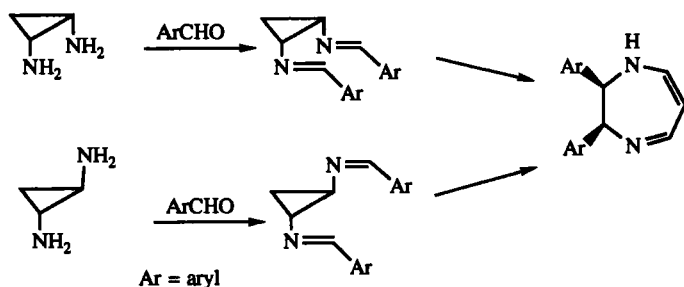
Two cyclization processes not involving condensation or nucleophilic displacement reactions have been used to prepare dihydrodiazepines.

Ethylenediamine adds to buta-1,3-diyne to give a high yield of 5-methyl-



dihydrodiazepine (69JOC999, 69ZC143). The same product has also been obtained from the addition of ethylenediamine to 1-dialkylaminobut-1-en-3-yne; in this case 1,3-addition is accompanied by elimination of a dialkylamine (83JOU1388, 83ZOR1541).

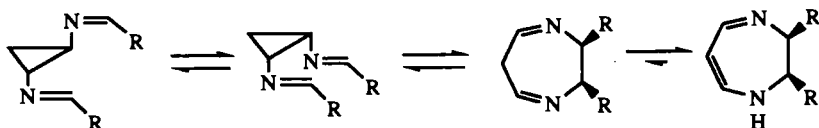
In the other process bisanils of 1,2-diaminocyclopropanes are heated and undergo a Cope rearrangement, thereby forming 2,3-diaryldihydrodiazepines (65CB2691; 65CB2701; 65TL51; 77TL2709; 83LA1209).



Spectra confirm the structure of the products; in the case of $\text{Ar}=\text{Ph}$, it has also been prepared by an alternative route, from *meso*-1,2-diamino-1,2-diphenylethane and acetylacetone (65CB2701) or 1,5-diphenyl-1,5-diazapentadienium perchlorate (77TL2709). In the case of the *cis*-diamines the intermediate bis-anil is usually neither isolable nor even detectable by NMR spectroscopy (77TL2709; 83LA1209), although in one case it has been isolated and converted into a dihydrodiazepine by heating (83LA1209). *trans*-Dianils, on the other hand, are more stable and readily isolated, and require strong heating to undergo the Cope rearrangement. When the aryl groups are replaced by *t*-butyl groups the resultant diimines are more stable. The *cis*-diimine is isolable and only rearranges slowly at 100°C ; the *trans*-diimine does not undergo rearrangement up to 170°C (77TL2709). This is presumably because of the steric crowding introduced in the formation of the 2,3-di-*t*-butyldihydrodiazepine (77TL2709).

The bishydrobromide of *trans*-1,2-diaminocyclopropane provides a dihydrodiazepine when kept with benzaldehyde in acetate-buffered methanol at 20°C (83LA1209).

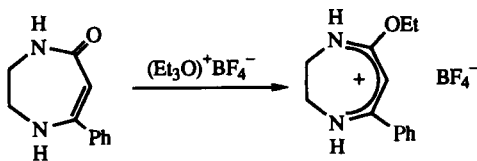
The reaction sequence for these reactions is thought to be as follows (65CB2701).



It is suggested that the overall equilibrium is controlled by the last step; all work on dihydrodiazepines shows that equilibria between the two tautomeric forms lies almost completely on the side of the conjugated form. In support of this it was shown that the bisanil of *trans*-2,3-diamino-1,1-diphenylcyclopropane does not rearrange thermally into a dihydrodiazepine (65CB2701). In this instance, the last step is prevented by the presence of two phenyl groups at the 6-position.

The diaminocyclopropanes and their salts have also served as precursors for the preparation of 2,3-cyclopropanodihydrodiazepines [77AG668, 77AG(E)643], which are of interest because they themselves undergo Cope rearrangements (see Section X).

Attempts to dehydrogenate 1,4-diazacycloheptane to a dihydrodiazepine failed (70MI1), but 1-methyl-2-oxodihydrodiazepines have been obtained by dehydrogenation of 2,3,6,7-tetrahydrodiazepines with benzoyl peroxide and *N*-bromosuccinimide (69JMC914), and a tetrahydrodiazepinone has been converted by alkylation into an alkoxydihydrodiazepinium salt (76GP2512510).

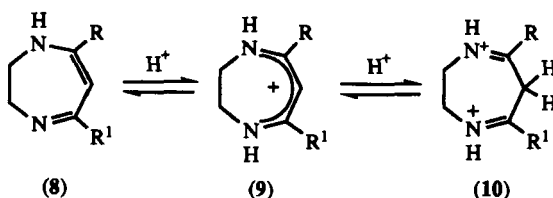


III. Stability of Dihydrodiazepines and Dihydrodiazepinium Salts

A. GENERAL COMMENTS

The dihydrodiazepinium monocations (9) are extremely stable. This is illustrated by the enormous pH range over which the monocation is the predominant species. The pK_a values for the equilibria with the related bases (8) are about 13–14 [40HCA1162; 66JCS(C)780], while spectra of

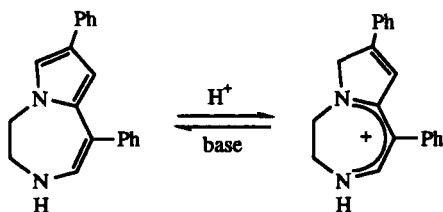
solutions indicate the absence of any notable contribution of the dication (10) in 40% sulfuric acid; only in >70% sulfuric acid do these dications predominate over monocations [UP1; 66JCS(C)780].



The base strength of the dihydrodiazepines (8) is further demonstrated by the fact that when they are kept in solution in chloroform at room temperature for some hours they bring about elimination of hydrogen chloride from the solvent and are thereby converted into the corresponding dihydrodiazepinium chlorides [66JCS(C)780].

The stability of the dihydrodiazepines and, even more so, of the dihydrodiazepinium salts is due to their delocalized systems of π -electrons; this is especially marked in the monocations wherein the system is symmetrical, and is an example of a vinamidinium system [76AG496;76AG(E)459] made even more stable by its being held in an almost planar configuration by the ring of which it forms part. Calculations based on p*K* data suggest a resonance energy of about 19 kcal · mol⁻¹ for these cations [72CI(L)335]. A similar calculation suggests that dihydrodiazepine bases have 8 kcal · mol⁻¹ less resonance energy than the corresponding cations, but this still leaves a resonance energy of perhaps 10–12 kcal · mol⁻¹ for the conjugated base structure (8), accounting for the preference of this structure over the unconjugated bisimine structure as in (3).

Some confirmation of these values is provided by the ready interconversion that takes place between a pyrroldiazepine and its perchlorate [78CC499; 80JCS(P2)1441]:



This acid–base equilibrium involves the interconversion of two distinct delocalized systems, a pyrrole and a dihydrodiazepinium cation. Pyrrole

has a resonance energy of $21 \text{ kcal} \cdot \text{mol}^{-1}$, very similar to that calculated for the dihydrodiazepinium cation. The ready interconversion of the above species tallies nicely with their having electronic systems of comparable stability.

This stability is also reflected in their chemical behavior. The electronic system resists breakdown, and, to use Armit and Robinson's classic phrase (25JCS1604), shows a great tendency to retain the type. This is particularly reflected in the way that these compounds often undergo substitutive rather than additive or destructive reactions, and is discussed further in Section VI.

Solutions containing only the dihydrodiazepinium monocations (9) are unaffected by aqueous permanganate, even after several days, but solutions in either strong acid or alkali that contain appreciable concentrations of, respectively, the dications or free bases decolorize permanganate solutions fairly rapidly.

Catalytic hydrogenation of 5-methyldihydrodiazepine over a prerduced platinum oxide catalyst in aqueous acetic acid, to give the corresponding hexahydrodiazepine, has been reported (69JOC999). A number of dihydrodiazepines have been reduced electrochemically, often providing unexpected products; this is discussed in Section XI.

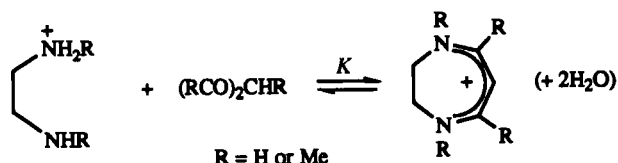
Attempts have been made to dehydrogenate dihydrodiazepines or their salts using a variety of methods (60CB264; 66MI1); not surprisingly, since such a reaction would convert a stabilized vinamidinium system into a cyclic $8\text{-}\pi$ -electron system having no special stabilization, the dihydrodiazepines (or their salts) were recovered unchanged.

5,7-Disubstituted dihydrodiazepines and dihydrodiazepinium salts resist hydrolytic cleavage over a wide range of pH values and are normally only hydrolyzed at very high or very low pH (56JCS2597). With aqueous sodium hydroxide and benzoyl chloride cleavage ensues and dibenzoyl ethylenediamine is formed [66JCS(C)780]. 6-Nitro and 6-amino derivatives are stable in acid but are hydrolyzed by dilute alkali; in the former case the nitro group may lower the basicity of the dihydrodiazepine and increase its susceptibility to nucleophilic attack [70JCS(C)617]. *N,N*-Diphenyl-5,7 dimethyldihydrodiazepinium salts also decompose in alkali [60CB264; 66JCS(C)93]. In this case it is not possible to obtain any corresponding dihydrodiazepine base and the only available course of reaction with alkali inevitably entails ring-opening. An oxoenamine, $\text{MeCOCH}=\text{CMeNPh}(\text{CH}_2)_2\text{NHPh}$, has been isolated [69JCS(C)1081].

In contrast, dihydrodiazepines lacking 5,7-substituents are readily hydrolyzed in dilute mineral acid [58JCS118; 71JCS(B)795, 71JCS(B)1529; 75JCS(P1)1260].

B. STABILITY CONSTANTS AND HYDROLYSIS EQUILIBRIA

The marked stability of dihydrodiazepines and dihydrodiazepinium salts and their ready formation in aqueous solution are reflected in the stability constants for their formation. These have been measured [68JCS(B)1536] for a range of methyl-substituted salts and refer to the following equilibrium:



The equilibrium constants for 25°C, ignoring the water formed, are tabulated in approximate order of stability in Table I.

When few methyl groups are present, stability is high, with values exceeding 10^9 . (Inclusion of water concentration would raise this to 10^{13} .) The 5,7-dimethyl compound, which is the most studied dihydrodiazepine derivative, is not in fact the most stable. The most striking values, however, are those for the highly substituted compounds. The last two compounds listed have never been isolated and are formed in no more than very small amounts even at the most favorable pH values. Their stability constants are very rough values based only on observed UV absorption spectra. A 1,4,5-trimethyl-6-phenyldihydrodiazepinium salt has been

TABLE I
STABILITY CONSTANTS OF DIHYDRODIAZEPINIUM CATIONS

Compound no.	Positions of methyl substituents					K
	4	5	6	7	1	
(i)	—	—	—	—	—	2.5×10^9
(ii)	Me	—	—	—	Me	3.2×10^9
(iii)	Me	—	Me	—	Me	7×10^8
(iv)	—	—	Me	—	—	1.3×10^6
(v)	—	Me	—	Me	—	3.4×10^6
(vi)	Me	Me	—	Me	Me	1.5×10^4
(vii)	—	Me	Me	Me	—	$< 10^5$
(viii)	—	Me	Me	—	—	1.0×10^3
(ix)	Me	Me	Me	—	Me	$\sim 10^{-3}?$
(x)	Me	Me	Me	Me	Me	$\sim 10^{-5}?$

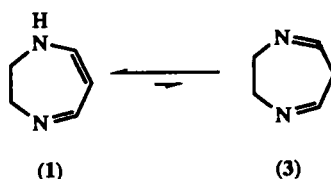
made under nonaqueous conditions and isolated, however, albeit contaminated by *N,N'*-dimethylethylenediamine perchlorate [81JCS(P1)726]. Clearly this ring system is made less stable by crowding of substituents. This leads to steric distortion of the vinamidinium system; X-ray structure determinations provide direct evidence of such distortion caused by vicinal substituents [91JCS(P2)1563].

The parent compound (i), (7), is very difficult to prepare by the standard method from malonaldehyde and ethylenediamine [68JCS(B)1536], although it is one of the most stable, but can be prepared readily from imines of malonaldehyde and ethylenediamine under nonaqueous conditions (73S791). This is apparently because, despite its thermodynamic stability, it is hydrolyzed readily in aqueous solution. (Thus chromatographic separations, successful with many dihydrodiazepines, can result in progressive loss of material.) In contrast, derivatives substituted at positions 5 and 7 are hydrolyzed only very slowly, if at all, nucleophilic attack at these positions being sterically inhibited by the substituents.

IV. Structure

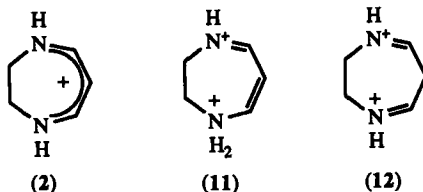
A. GENERAL COMMENTS

As discussed earlier, dihydrodiazepine bases exist almost exclusively as the conjugated tautomers (1), although facets of their chemistry suggest that, at least in the case of many that are substituted in the 5,6, and/or 7 positions, there must be some small contribution from the unconjugated tautomer (3) (see Section VIII).



Such contributions are small enough to make them hitherto undetected by spectroscopic methods. Rapid tautomeric exchange of hydrogen atoms between the two nitrogen atoms takes place, however, since NMR spectra in a variety of solvents show that for symmetrically disubstituted dihydrodiazepines the 2 and 3 positions are equivalent as are the 5 and 7 positions (65CB2701; 68MI1). *N*-substituted dihydrodiazepines must exist in the conjugated form.

Monoprotonation takes place at nitrogen to give the dihydrodiazepinium cation (2), which has a stabilized vinamidinium system [76AG496; 76AG(E)459]; their structures are confirmed by spectroscopic and X-ray data, as outlined in Sections V and IV.B, respectively.



Protonation of the monocations might take place at a nitrogen atom to give dications such as (11) or alternatively at the 6-position to give dications such as (12). Spectroscopic evidence shows that the latter is certainly the predominant species in solutions of dihydrodiazepines in strong acid [66JCS(C)780], although hydrogen-deuterium exchange takes place in deuterio-acids both at the nitrogen atoms and at the 6-position (65CB2681, 65CB2701, 65TL51; 66M11).

B. X-RAY STUDIES

The X-ray structures of a number of dihydrodiazepinium salts, namely the unsubstituted compound [84AX(C)1740], its 5,7-dimethyl derivative [80JCS(P2)74; 84M11], its 5,7-diphenyl derivative [91AX(C)1290], its 1,4-diphenyl-6-cyclopropyl derivatives (79CSC445), several 6-bromo derivatives with various other substituents [90AX(C)1248; 91JCS(P2)1563], and also a 4,5-pyrrolo-fused derivative [79AX(B)1175], have been determined.

The structure of the dihydrodiazepinium ring is consistent through all these examples. It consists of a delocalized vinamidinium portion [N(4),C(5-7),N(1)], which has a flat helical structure and whose ends are linked by a dimethylene bridge that takes up a half-chair shape. Bond lengths in the vinamidinium portion (N—C, 1.300–1.335 Å; C—C, 1.385–1.400 Å) are consistent with an essentially completely delocalized π -electron system. The ring angles in this part of the ring ($\sim 127^\circ$) are markedly increased from the 120° normal for sp^2 carbon atoms; compensation for this expansion is provided by extra twisting away from a standard gauche conformation in C(2),C(3). Some measure of electronic interaction from 5- or 7-phenyl substituents into the vinamidinium system, inferred

from chemical and spectroscopic observations, is supported by bond lengths in such compounds [91AX(C)1290, 91JCS(P2)1563]. Comparison of the detailed structures of the bromo compounds demonstrates the effects of steric crowding caused by geminal substituents [91JCS(P2)1563].

V. Spectra

A. ELECTRONIC SPECTRA

The electronic spectra of dihydrodiazepinium salts are characterized by an intense absorption ($\epsilon=15,000\text{--}25,000$), commonly between 300 and 360 nm. The unsubstituted cation absorbs at 331 nm ($\epsilon=14,300 \pm 200$). The related bases absorb with somewhat reduced intensity at a slightly shorter wavelength.

In the alkyl-substituted dications there is no appreciable absorption above 200 nm, but in the case of the 5,7-diphenyl-substituted dication there is a band at ~ 290 nm ($\epsilon=23,500$). The large change on going to the dications is due to the loss of the conjugated vinamidinium system when it is protonated to form a dication.

The absorption in the dihydrodiazepinium monocations has been ascribed to a $\pi\text{--}\pi^*$ transition (68MI1; 71MI2). It occurs at a similar wavelength and intensity to the $\pi\text{--}\pi^*$ transitions in open-chain *cis*-2-iminoenamines but not to those of pyrimidines, this being in accord with the lack of complete cyclic electronic interaction in the dihydrodiazepines (68MI1).

Substituent groups have a generally regular effect on the position of the absorption maxima in dihydrodiazepinium cations. Thus methyl groups at the 1- and 4-positions or at the 6-position cause bathochromic shifts of about +6 and +22 nm, respectively, whereas at the 5,7-positions they cause (hypsochromic) shifts of about -4 nm [66JCS(C)93; 68JCS(B)1536; 76JCS(P1)1784]. These effects are additive for compounds substituted by more than one methyl group. They may be compared with similar shifts in azulenes, with methyl groups substituted at sites of high or low π -electron density causing, respectively, bathochromic or hypsochromic shifts. Other alkyl groups have similar effects. There are similar regular changes in the intensity of absorption, which is raised by methyl groups at the 1-, 4-, 5-, or 7-positions but lowered by a methyl group at the 6-position [68JCS(B)1536].

Empirically calculated values of the extinction coefficients of methyl-substituted dihydrodiazepinium salts based on the 6-methyl derivative as standard are generally in good agreement with experimental values but the experimental value for the parent unsubstituted salt is markedly higher

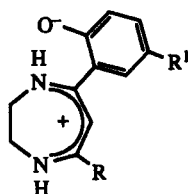
than the estimated figure, possibly reflecting the absence of distortion of the π -system caused by substituents (cf. Section VIII) [75JCS(P1)1260].

Phenyl substituents at all sites in the vinamidinium system cause bathochromic effects, amounting to ~ 14 nm at the 5,7-positions and ~ 25 nm at the 1-,4-, or 6-positions [60CB264; 67ZN(B)722; 69JCS(C)1081]. These bathochromic shifts are, however, diminished if there is a methyl group vicinal to the phenyl group, because of steric interference between the adjacent groups that forces the phenyl group far enough out of coplanarity with the dihydrodiazepinium ring to reduce electronic interactions between the rings [66JCS(C)93; 69JCS(C)1081]. 6-Aryl substituents appear to lower the extinction coefficient [78JCS(P1)1453; 81JCS(P1)726].

Other substituents at the 6-position also make marked and fairly regular contributions to the UV spectra of dihydrodiazepinium salts. Halogen atoms [58JCS118; 69JCS(C)1081; 69JCS(C)1449], arylazo (71LA207), alkoxy [69JCS(C)1081] and amino groups [70JCS(C)617] have marked bathochromic effects, lost in the case of amines when the amino group is protonated; 6-nitro groups show small hypsochromic effects [66JCS(C)93; 67CC637, 67JCS(C)2436; 70JCS(C)617].

An aqueous solution of 5,7-dimethyldihydrodiazepinium perchlorate and copper(II) sulfate has been used as an inexpensive and effective optical filter (90AJC1231).

The hydroxyphenyldihydrodiazepine derivatives shown below are fluorescent as solids when irradiated at 365 nm (85S339). They are also fluorescent in viscous solutions but not in solution in organic solvents.



B. INFRARED SPECTRA

The infrared spectra of dihydrodiazepinium salts are complex but there are several characteristic bands [68JCS(B)1536]. In the 3000 cm^{-1} region $\bar{\nu}_{\text{NH}}$ shows as a medium to strong band at $\sim 3500\text{ cm}^{-1}$. Hydrogen atoms at the 5-, 6-, or 7-positions give rise to a weak $\bar{\nu}_{\text{C-H}}$ band at $3050\text{--}3100\text{ cm}^{-1}$; alkyl $\bar{\nu}_{\text{C-H}}$ bands at $\sim 2900\text{ cm}^{-1}$ are also weak. When there are hydrogen

atoms at positions 5 or 7 there is a fairly strong band at $1215\text{--}1255\text{ cm}^{-1}$, which is absent if these positions carry substituents; they may be due to C—H deformations. All spectra of dihydrodiazepinium salts show three strong bands at $1610\text{--}1650\text{ cm}^{-1}$, at $1510\text{--}1575\text{ cm}^{-1}$, and at $1305\text{--}1335\text{ cm}^{-1}$, the first two apparently due to coupled multiple-bond stretching and the third to $\bar{\nu}_{\text{C-N}}$.

The infrared spectra of dihydrodiazepine bases show bands at $3150\text{--}3190\text{ cm}^{-1}$ (NH), no normal C=N absorption, and a characteristic absorption between 1500 and 1600 cm^{-1} [67JCS(C)2400; 76IJC(B)1004].

C. NUCLEAR MAGNETIC RESONANCE SPECTRA

The NMR spectra of dihydrodiazepines and their mono- and dications accord completely with the assigned structures [65CB2701; 66JCS(C)780; 68MI1, 68TL4983; 71MI2; 73JCS(P2)1729; 76T2339]. The most characteristic feature of the ^1H -NMR spectra of the bases and the monocations is the markedly different positions at which protons at the 5- and 7-positions (δ 7.4–7.8 for N-unsubstituted cations) and at the 6-position (δ 5.0–6.0) appear. The corresponding shifts for dihydrodiazepine bases (δ 6.5–7.0 and δ 4.4–4.8) are at lower frequency (higher field), in accord with the absence of positive charge. The large differences between the 5,7-positions and the 6-position can be correlated with the large difference in electron density and nucleophilicity at these sites, as discussed later in Section VI.

In a detailed study [73JCS(P2)1729] of the ^1H -NMR of a number of dihydrodiazepinium salts the magnitude of the coupling between the N—H and 6-C—H confirmed both that the unsaturated portion of the molecule is effectively planar and that the dimethylene bridge must take up a half-chair conformation. The coupling constants $J_{5,6(6,7)}$ and $J_{4,5(1,7)}$, which are both $\sim 8.0\text{ Hz}$, also provide evidence for the almost complete delocalization of electrons over the conjugated chain. Dihydrodiazepinium cations that do not have large substituents on the 2,3-positions undergo rapid ring inversion at room temperature [73JCS(P2)1729; 75JHC611; 82ZN(B)1187]; the signals for the 2,3-methylene groups appear as singlets at room temperature but as AA'BB' multiplets at lower temperatures. The coalescence temperatures occur at about -20° to -40°C and appear to depend upon the bulk of substituents in the unsaturated portion of the ring, whereas electronic factors appear to have little effect [73JCS(P2)1729]. Crowding of substituents in the vinamidinium system, which also appears to affect its structure and chemical properties (see Sections IV,B, and VI,F and VIII, respectively), appears to lower the activation energy for ring inversion [73JCS(P2)1729]. Further evidence for such vicinal crowding comes

from the spectra of phenyl groups attached to the conjugated part of the ring; in the absence of adjacent substituent groups they provide multiplet signals, but they appear as singlets when vicinal methyl groups are present [73JCS(P2)1729]. Large substituents at the 2,3-positions inhibit ring inversion. Thus *cis*-2,3-aryl derivatives show coalescence temperatures for the methylene groups $\geq 50^\circ\text{C}$, whereas the spectrum of the *cis*-2,3-di-*t*-butyldihydrodiazepinium cation is unchanged up to 100°C [77AG668, 77AG(E)643].

A detailed study of the ^{13}C -NMR spectra of a variety of dihydrodiazepinium salts has been carried out (76T2339), and an investigation has also been made of the effect of a range of 6-substituents on their spectra [76ZN(B)1641]. The spectra emphasize the alternating polarity along the conjugated chain, the signals for 6-C appearing at $\delta \sim 90$ ppm and those for 5,7-C at $\delta \sim 160$ ppm. It is intriguing to note that the 6-C signal appears at a position very similar to that of the 3-C of the isoelectronic pentadienide anion, thus nicely demonstrating the ironical fact that the dihydrodiazepinium cation is an electron-rich cation. Application of an empirical relationship (72MI1) provides an estimated electron density of ~ 1.3 electrons at 6-C and ~ 0.8 electrons at 5,7-C, suggesting that the π -electrons are predominantly associated with the nitrogen atoms (~ 1.6 electrons each).

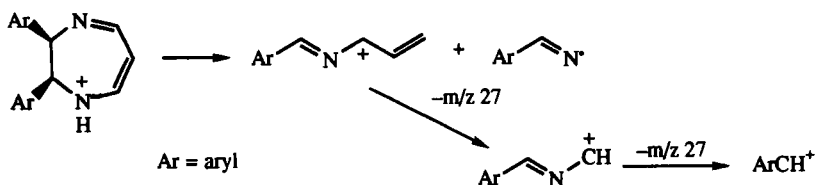
Variable temperature studies again show the ring inversion (76T2339). They also indicate that a 2-methyl group shows equal preference for the quasi-axial or quasi-equatorial positions, presumably because there are no other axial substituents to cause 1,3-diaxial interactions.

The chemical shifts caused by different substituent groups closely resemble those observed for benzene derivatives [76T2339, 76ZN(B)1641].

As with ^1H -NMR the effect of vicinal groups on the conjugation between the vinamidinium system and substituent phenyl groups is clearly evident [76T2339; 81JCS(P1)726; 86LA1387], resulting in a lowered value for $\Delta\delta$, the difference $[\delta(p) - \delta(m)]$ between the chemical shifts associated with the *p*- and *m*-carbon atoms in the phenyl ring. Thus, in the case of 1-methyl-5,7-diphenyldihydrodiazepinium perchlorate $\Delta\delta$ for the 5-phenyl group = 2.74, whereas for the 7-phenyl group $\Delta\delta = 1.90$ (86LA1387). Phenyl substituents at the 5,7-positions interact by donating electrons into the vinamidinium system, resulting in $\delta(p) > \delta(m)$. In contrast, phenyl substituents at the 1-, 4-, or 6-positions interact by withdrawing electrons; hence $\delta(p) < \delta(m)$. Thus for the 6-phenyl derivative, $\Delta\delta = -2.49$ [81JCS(P1)726]. The $\Delta\delta$ value is numerically smaller when further phenyl groups are introduced at the 1- and 4-positions, $\Delta\delta$, 6-Ph, -2.49 ; 1,6-diphenyl, -2.04 ; 1,4,6-triphenyl, -1.28 [81JCS(P1)726]. This presumably reflects competition from the additional phenyl substituents for the electrons from the vinamidinium group.

D. MASS SPECTRA

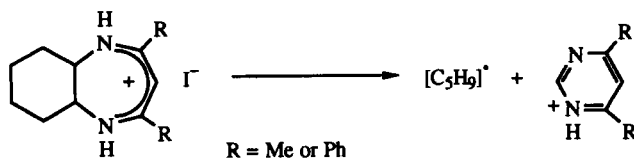
In an early study using electron impact (ei) mass spectrometry it was found that 2,3-diphenyldihydrodiazepine bases gave intense molecular ions and that the major breakdown pathway involves loss of the N(1)—C(2) fragment (65CB3479).



Sequential cleavage of the initially formed fragment cation accounts for most of the other major peaks in the spectrum; each of these processes is supported by the observation of metastable peaks. Alternatively, the molecular ion can break down by elimination of an $\text{ArCH}_2\cdot$ fragment derived from C(2); this route generally gives rise to low-intensity peaks (<5%), but can be important in certain cases [e.g., for Ar = 1-naphthyl, $(\text{M}-\text{ArCH}_2)^+ = m/z$ 207 (41%)] (82MI1).

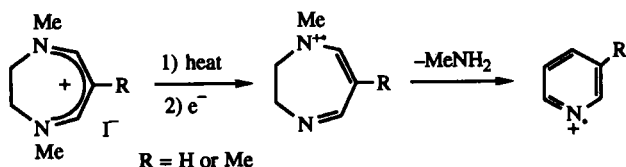
Dihydrodiazepinium perchlorates do not give reproducible mass spectra under ei conditions, presumably owing to poor volatilization (77AJC365). However, the corresponding iodides apparently dissociate on heating and give rise to good mass spectra in which the molecular ion usually corresponds to that of the free base [77AJC365; 81JCS(P1)726]. In some cases, and especially if the 1-, 4-, and 6-positions are blocked by substituents, the molecular ion of the dihydrodiazepinium cation may be observable.

An extensive range of alkyl- and aryl-substituted dihydrodiazepinium iodides was studied [77AJC365; 81JCS(P1)726], and the major fragment ions of the 5,7-diphenyl derivative were analyzed by accurate mass measurement. The most intense breakdown peak in most of the spectra again corresponds to loss of the N(1)—C(2) fragment. The alternative loss of the C(2) fragment mentioned above was important only for 2,3-cyclohexano derivatives, in which the usual process cannot function. In these cases loss of $\text{C}_5\text{H}_9\cdot$ occurs [i.e., C(2), plus the four unfused carbon atoms of the cyclohexano ring]. The residue may be written as a pyrimidinium species:



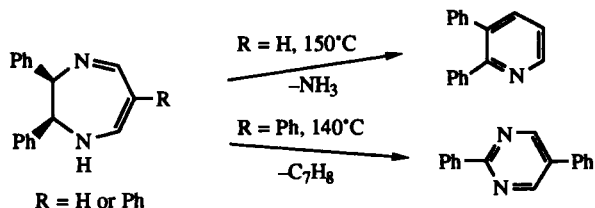
An alternative, but less favored, breakdown from the dihydrodiazepine molecular ion, which is nonetheless generally observed, involves cleavage of the N(1)—C(7) fragment (77AJC365); such loss of cyanides is a favorable process in the mass spectra of many nitrogen heterocycles. Simple cleavage of a substituent can also be important, especially for alkyldihydrodiazepines, and for those that have an electronegative substituent at the 6-position (77AJC365).

Anomalous spectra are given by the 1,4-dimethyl and 1,4,6-trimethyl derivatives (77AJC365). Iodide-induced N-demethylation is followed by loss of methylamine to give intense fragments that may be represented as pyridine derivatives:



Recently a series of dihydrodiazepinium perchlorates and iodides has been subjected to fast-atom bombardment mass spectroscopy (thioglycerol or glycerol matrix) (UP 2). In all cases intense molecular ions due to the dihydrodiazepinium cations are observed, together with weak higher-mass peaks due to electrostatic clusters of $[(\text{cation})_n \cdot (\text{anion}_{n-1})]^+$ [87JCS(P2)1129]. Breakdown peaks are also of low intensity but generally follow the same pattern as in the corresponding *ei* spectra.

It is of some interest that the ring contractions giving rise to pyrimidine or pyridine derivatives may occur as simple thermal processes, for example (77TL2709; 83LA1230).



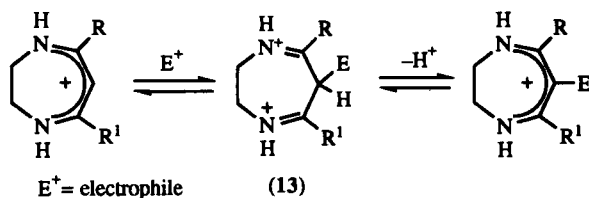
When the 2,3-diphenyldihydrodiazepine is heated at 150°C in bromobenzene for 40 h 2,3-diphenylpyridine is formed in quantitative yield, whereas under similar conditions the 2,3,6-triphenyl derivative gives 2,5-diphenylpyrimidine in 70% yield (83LA1230). Mechanisms have been proposed (83LA1230), but the reason for the dichotomy is not understood. (See also Section X.)

VI. Electrophilic Substitution Reactions

A. GENERAL COMMENTS

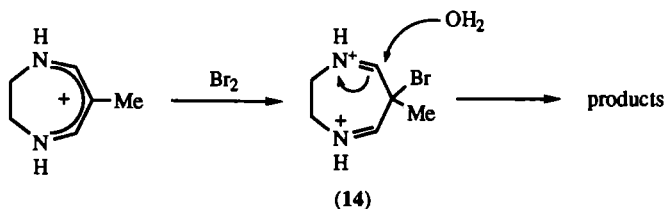
Perhaps the most characteristic reaction of dihydrodiazepinium salts is their susceptibility to electrophilic substitution at position 6. Thus they are readily deuteriated [64JCS2195; 65CB2701; 68JCS(B)1572; 71JCS(B)795], halogenated [58JCS118; 66JCS(C)93, 66JCS(C)780; 69JCS(C)1449; 75JCS(P1)1260, 75JCS(P2)325; 76IJC(B)1004; 89LA133], and nitrated [67CC637, 67JCS(C)2436; 68CI(L)130; 70JCS(C)617; 75JCS(P1)1260] and couple with diazonium salts (70CC1320). Electrophilic substitution occurs under conditions similar to those used for benzene derivatives. Indeed the kinetics of the halogenation (64JCS2195; UP3) and nitration (UP3) reactions closely resemble those of benzenoid compounds, in the case of halogenation resembling those for activated benzene derivatives, such as phenols or amines. Kinetic studies (see Section VI,B) indicate that the dihydrodiazepinium cation is indeed involved in these electrophilic substitutions, so that the nitration reaction represents an example of electrophilic attack by a cation on another cation.

The mechanism for these electrophilic substitution reactions involves formation of a dication intermediate (13) which, as in the case of benzenoid substitution reactions, loses a proton and reverts to the original stable system.



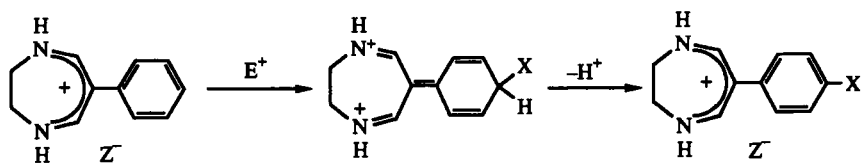
Similar stable intermediate dication structures cannot be drawn for electrophilic attack at the 5- or 7-positions. This is reflected in the enormous difference in reactivity toward electrophiles between the 6-position and the 5- and 7-positions [71JCS(B)795, 71JCS(B)1529]. Kinetic studies of the bromination [71JCS(B)1529] and deuteration [71JCS(B)795] of dihydrodiazepines and their salts indicate a ratio of reactivities for these positions of at least $1 : 10^9$, and probably greater. Indeed 6-methyldihydrodiazepinium salts undergo attack by bromine at the 6-position, despite the presence of the substituent group at that position, rather than at the 5(7)-position [71JCS(B)1529]. The resultant products are hydrolysis products,

since the dication intermediate (14) has no mesomeric stabilization and cannot gain such stabilization by loss of a proton, and, as a bisiminium salt, is readily hydrolyzed.



When 6-methyldihydrodiazepinium salts are kept in deuteriotrifluoroacetic acid for up to 10 days no hydrogen–deuterium exchange can be detected at the 5- and 7-positions [71JCS(B)795].

This reactivity can be transmitted to aryl substituents at the 1-, 4-, and 6-positions. Thus the 6-phenyldihydrodiazepinium cation can be brominated or nitrated at the *p*-position of the phenyl group [81JCS(P1)726].



Phenyl substituents at the 5- or 7-positions do not undergo such electrophilic substitution reactions. As mentioned in Section V,C, electronic interaction between phenyl substituents and the vinamidinium system appears to be into phenyl groups at the 1-, 4-, or 6-positions, but into the vinamidinium system from phenyl groups at the 5- and 7-positions.

At one time nonbenzenoid compounds that underwent electrophilic substitution reactions similar to those of benzene were described as “quasi-aromatic” (55JA4301), and this term was applied to dihydrodiazepinium salts [64CI(L)1760]. Because of the unsatisfactory nature of this term, the tendency to undergo substitution rather than addition reactions has been described instead as “regenerative” or “meneidic” [71MI1; 72AG447, 72AG(E)404]; dihydrodiazepinium salts are thus examples of compounds having regenerative or meneidic character.

Dihydrodiazepinium cations also undergo N-alkylation (86LA1387).

B. REACTION KINETICS

The similarity of behavior between the meneidic dihydrodiazepines and their salts and activated benzene derivatives such as anilines and phenols extends to reaction mechanisms, as indicated by kinetics. In aqueous solution bromination is a bimolecular reaction between dihydrodiazepinium cations and bromine molecules [64JCS2195; 71JCS(B)1529]. The leaving bromide ion is still present in the transition state and, as in many (but not all) brominations of activated benzene derivatives, the rate-determining step is the initial attack that leads to formation of the intermediate σ -complex (13). Steric factors play a large part in the rates of bromination of dihydrodiazepinium salts in methanol, reaction being slower when substituents are present at the adjacent 5- and 7-positions; this is increasingly so the larger the size of these substituents (89LA133). Substituents further removed from the site of bromination may also affect the rate; even substituents at the remote 2-position do so, and this has been rationalized in terms of an initial approach by the attacking bromine at the electron-rich 1,4-positions (89LA133).

The initially produced 6-bromo derivative can be further brominated to give a 6,6-geminally dibrominated species (64JCS2195). This reaction also begins by attack of bromine on the bromodihydrodiazepinium cation (although at a very much slower rate), but a dependence of the rate upon inverse of the bromide ion concentration shows that the rate-determining step this time is not attack by bromine, but decomposition of the intermediate. The reaction is accelerated by increase of pH, but the alternative explanation of a reaction involving bromination of bromodihydrodiazepine base is untenable, because its temperature dependence would require a negative activation energy (which is improbable). This effect of pH must arise therefore from loss of a proton by the intermediate. The final products are those formed by hydrolysis of the unconjugated dibromo compound, which must be the rate-determining step. The bromination of the bromodihydrodiazepinium salt does not take place at all in a solvent free from water [75JCS(P2)325].

Other 6-substituted dihydrodiazepinium salts may also be brominated. Kinetic measurements show that 6-methyl derivatives undergo addition of bromine at position 6 in a fast reaction between bromine molecules and dihydrodiazepinium cations [75JCS(P2)325]. The bromination of both 6-bromo and 6-methyl derivatives can be accommodated within a single reaction scheme, but the rate-determining steps are different for the two types of compounds. For 6-methyl derivatives the initial bromination is rate-determining, whereas for the 6-bromo derivatives the subsequent hydrolysis is rate-determining [75JCS(P2)325].

In contrast 6-phenyldihydrodiazepinium salts are brominated at the *p*-position of the phenyl group (see also Section VI,F); rates are generally slower than for brominations taking place in the dihydrodiazepinium ring (89LA133). Again, substituents affect the rates. 5,7-Methyl substituents prevent reaction by inhibiting coplanarity of the rings, and, surprisingly, methyl groups at the 2-position, although separated by seven atoms from the reaction center, cause an appreciable lowering of the rate (89LA133).

Iodination of dihydrodiazepines by iodine in buffered aqueous solution is particularly illuminating. Under most conditions the reaction rate is inversely proportional to the iodide concentration in a way which shows that the rate-determining step is removal of the leaving proton from the intermediate (13). In agreement with this the reactions are subject to general base catalysis and show substantial kinetic deuterium isotope effects (64JCS2195). By adjusting the base catalyst and iodide concentrations, however, it is possible to make competitive the rates of conversion of the intermediate to iodo-product or the rates of reversion to the starting materials, and so to demonstrate that the mechanism is indeed a two-step mechanism (UP3). In this the behavior is exactly like that of *p*-nitrophenol when it is iodinated (62JA212).

Iodination also is accelerated by an increase of pH (UP3). There are two parallel reactions, one with a transition state of the composition of (13), derived from dihydrodiazepinium cation, and a second related to the first by loss of a proton. As both reactions are generally base-catalyzed, this missing proton is an N—H proton. It is, however, impossible in principle to say whether the proton loss takes place before or after iodination, because the iodinations are slow enough for all steps prior to transition-state formation to be effectively in equilibrium with one another. This situation nevertheless allows the rate to be treated via the second reaction pathway as a rate of iodination of dihydrodiazepine base by iodine in a mechanism precisely like that of dihydrodiazepinium cation iodination, and so allows comparison of the reactivities of dihydrodiazepine base and dihydrodiazepinium cation.

On this basis it is possible to compare directly the reactivities in aqueous bromination and iodination of dihydrodiazepine base and dihydrodiazepinium cation with those of *para* substitution in aniline, phenol, and phenoxide ion (UP3), as shown in Table II.

The difference in reactivity between the dihydrodiazepine base and its cation is similar to that between the phenoxide anion and phenol, and is associated with the change in charge type. Ease of σ -complex formation is not directly relevant.

TABLE II
COMPARISON OF REACTIVITIES IN AQUEOUS HALOGENATION AT 25°C

Substrate	Iodination ($k_{\text{HPO}_4^{2-}}$)	Bromination (k_{Br_2})
Phenoxide anion	2.2×10^{6a}	—
5,7-Dimethyldihydrodiazepine base	1.5×10^6	—
Aniline	3.0×10^{2b}	$\sim 10^{9c}$
5,7-Dimethyldihydrodiazepinium cation	2.0×10^{-2}	4.4×10^6
Phenol	—	1.8×10^{5d}

^a Berliner (51JA4307).

^b Berliner (50JA4003).

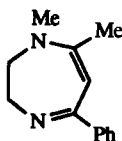
^c Bell and Ramsden (58JCS161).

^d Bell and Rawlinson (61JCS63).

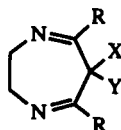
C. HALOGENATION AND PROTODEHALOGENATION

A wide variety of dihydrodiazepines and their monocations have been brominated either by bromine, most commonly in methanol, or by *N*-bromosuccinimide, to give their 6-bromo derivatives [58JCS118; 66JCS(C)93; 75JCS(P2)325; 69JCS(C)1449; 75JCS(P1)1260; 76IJC(B)1004; 89LA133]. In most cases exclusively monobromination resulted, the exceptions being 1,4-diphenyldihydrodiazepinium salts that were also brominated in the phenyl rings [66JCS(C)93; 69JCS(C)1449].

Also, in one case bromination of a 5(7)-methyl group rather than substitution at the 6-position has been reported [69JCS(C)1449]. This took place when 1,7-dimethyl-5-phenyldihydrodiazepine (**15**) was treated with bromine in methanol, and presumably results from the facts that, unlike *N*-unsubstituted dihydrodiazepines, this base has a fixed structure, incapable of tautomeric rearrangement, and in this structure the 7-methyl group is activated by conjugation with the azomethine group.



(15)



(16)

Not surprisingly substituents at the 5- and 7-positions slow down the bromination reactions, presumably by steric hindrance; unexpectedly so

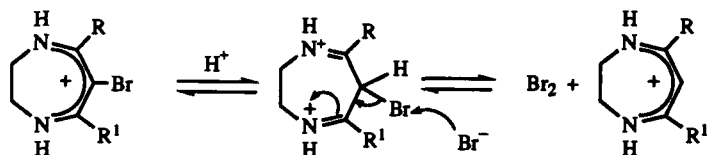
do substituents at the 2,3-positions (89LA133). A possible explanation for this is that initial attack on the cation occurs at a nitrogen atom, known to be the site of highest electron density, to form a complex, with the bromine atom then moving to the 6-carbon atom at which it forms a Wheland-type intermediate, which rapidly loses a proton to provide the isolated product. Substituents at the 2- and 3-positions could sterically hinder the initial approach of bromine toward the nitrogen atoms [76IJC(B)1004]. In accord with this, substituents at the 1,4-positions also appear to lower the reactivity.

Dihydrodiazepinium salts can be iodinated similarly by the use of *N*-iodosuccinimide [69JCS(C)1449; 75JCS(P1)1260]. Alternatively, some 6-iododihydrodiazepines are readily prepared by reaction of the corresponding 6-bromo compounds with sodium iodide in methanol [69JCS(C)1449]. (See also Section VIII.)

Chlorination is readily achieved by means of *N*-chlorosuccinimide [69JCS(C)1449; 75JCS(P1)1260; 76IJC(B)1004] but aqueous work-up of a reaction between chlorine and 5,7-dimethyldihydrodiazepine gave only 3,3-dichloropentane-2,4-dione [69JCS(C)1449]. It seems that chlorine readily dichlorinates the dihydrodiazepine to give a dichloro compound (**16**, R = Me, X = Y = Cl) which, having two azomethine groups but no stable delocalized electron system as in the parent compound, is very easily hydrolyzed.

Kinetic studies (see Section VI,B) indicated that similar dibromination of dihydrodiazepines could take place in aqueous solution but the dibromo products were not isolated owing to their ready hydrolysis (64JCS2195). The dibromo compound (**16**, R = Ph, X = Y = Br) and the bromochloro compound (**16**, R = Ph, X = Br, Y = Cl) were obtained by bromination of the appropriate monohalogenodihydrodiazepines in dry benzene [69JCS(C)1449]. These dihalogeno compounds were debrominated immediately to monohalogenodihydrodiazepinium salts in dilute aqueous acid.

6-Bromodihydrodiazepinium halides, but not, for example, perchlorates or trifluoroacetates, are protodebrominated in strong acids [69JCS(C)-1449]. Dilution with water of the solutions in strong acid causes reformation of the 6-bromo compounds but the debrominated products remain if the dilution is made with aqueous thiosulfate. These reactions are dependent on the following equilibria:



In keeping with this mechanistic picture and with the known relative tendencies of different halogens to form halonium ions, 6-iododihydrodiazepinium salts are dehalogenated more readily in acid than their bromo analogs [64JCS2195; 74CI(L)525], whereas 6-chlorodihydrodiazepinium salts undergo dechlorination extremely slowly, if at all [74CI(L)525].

D. NITRATION

5,7-disubstituted dihydrodiazepinium salts are readily nitrated at the 6-position [67CC637, 67JCS(C)2436; 68CI(L)130; 70JCS(C)617]. Kinetic studies show that the dihydrodiazepinium monocation is indeed the substrate species involved in the reaction, the reagent being the nitronium ion (UP3).

Nitric acid alone, or nitric acid-sulfuric acid mixtures are effective reagents for dihydrodiazepinium salts without phenyl substituents, but nitric acid-sulfuric acid mixtures are unsuitable for phenyl-substituted compounds since under these conditions the phenyl as well as the dihydrodiazepinium rings are nitrated [70JCS(C)617]. It did not prove possible to isolate the 6-nitrodihydrodiazepine bases owing to their ready hydrolysis [70JCS(C)617].

Attempts to prepare the 6-nitro derivative from the unsubstituted dihydrodiazepinium perchlorate (**7**) failed, apparently because, in contrast to 5,7-disubstituted salts, (**7**) is decomposed irreversibly by mineral acids [75JCS(P1)1260].

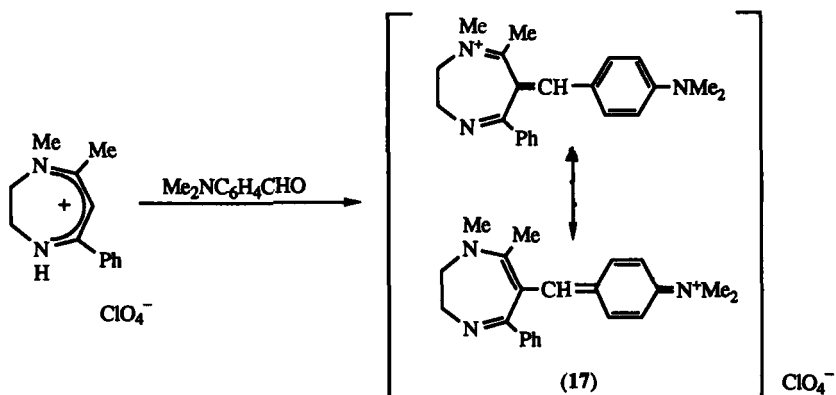
E. OTHER REACTIONS

Other reactions with electrophiles that have been recorded are those with aryldiazonium salts, with *p*-dimethylaminobenzaldehyde, and with alkyl halides.

Aryldiazonium salts react at once with dihydrodiazepinium salts and provide a further example of a reaction between two cations, but the coupling products are hydrolyzed very readily and the products isolated were α -arylazo derivatives of 1,3-diketones (70CC1320). 6-Arylazo-*N,N'*-disubstituted dihydrodiazepinium salts have, however, been obtained by condensation of 2-arylazo derivatives of oxomalonaldehyde with ethylenediamine (75HCA2283) or *N,N'*-disubstituted ethylenediamines (71LA207) or of ethylenediamine with 2-arylazo derivatives of 2-oxo-1,3-diketones (78JIC577).

A dihydrodiazepinium salt has also been coupled at its 6-position with

p-dimethylaminobenzaldehyde to give the purple mesomeric product (17), which turns yellow in trifluoroacetic acid and is reprecipitated from such solutions by addition of methanol.



All the reactions hitherto described in Section VI have provided 6-substituted products, although it was pointed out that initial attack by an electrophile could involve the electron-rich 1,4-positions. *N*-Alkylation at the 1,4-positions occurs when *N*-unsubstituted dihydrodiazepinium salts are treated with iodomethane or iodoethane and potassium carbonate in dimethylformamide (86LA1387).

F. REACTIONS OF 6-ARYLDIHYDRODIAZEPINIUM SALTS

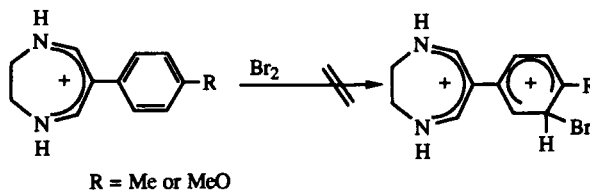
The characteristic reactivity toward electrophiles of the vinamidinium system can be transmitted to the *p*-positions of phenyl groups at the 1-, 4-, and 6-positions, but not to phenyl groups at the 5,7-positions.

5,7-Dimethyl-1,4-diphenyldihydrodiazepinium perchlorate is brominated not only in the seven-membered ring, but also at the *o*- and *p*-positions of the phenyl rings [69JCS(C)1449]. On the other hand 1,4-di(*p*-methoxyphenyl) dihydrodiazepinium perchlorate is brominated only at the 6-position and not in the aryl rings [81JCS(P1)726].

The 6-phenyldihydrodiazepinium cation is readily brominated at room temperature to give the 6-*p*-bromophenyl derivative [81JCS(P1)726]. At a naive level this result would seem to indicate the unusual feature of activated substitution at the *p*-position of a benzene ring brought about by a substituent 'onium group, but the present 'onium group is in fact an electron-rich species. Analogs with substituents at the 1-, 2-, 3, or 4-

positions of the seven-membered ring have been brominated in the same way, but substituents vicinal to the interannular bond inhibit such a reaction; for example, 5-methyl-6-phenyl- and 6-(*o*-tolyl)-dihydrodiazepinium salts do not undergo this reaction [81JCS(P1)726]. The mechanism of the reaction (see Section VI,A) requires double-bond character in the interannular bond and consequent coplanarity of the two rings; this is hindered by the presence of vicinal substituents. 6- α -Naphthyl and 6- β -naphthyl analogs are also readily brominated but the 6-(biphenyl-4-yl) analog does not react [81JCS(P1)726], presumably because formation of a Wheland-type intermediate is inhibited because it involves loss of the delocalization energy of two aryl rings as well as that of the vinamidinium system.

The 6-*p*-tolyl and 6-*p*-methoxyphenyl analogs, despite the presence of activating substituents, do not react with bromine [81JCS(P1)726]. Presumably attack at the *o*-positions is sterically hindered, whereas attack at the *m*-positions, which should be activated by the vicinal electron-donating groups, would generate intermediates that could be destabilized by interaction between two adjacent positively charged systems:



Surprisingly 6-(*p*-hydroxyphenyl)- and 1,4-dimethyl-6-(*p*-hydroxyphenyl)-dihydrodiazepinium salts react readily with bromine, giving 6-(3-bromo-4-hydroxyphenyl) and 6-(3,5-dibromo-4-hydroxyphenyl) derivatives (86LA1380). It is thought that in these cases the intermediate is a cyclohexadienone rather than a doubly charged species as shown above (86LA1380).

Also surprisingly, the 6-(3¹-hydroxyphenyl) and 1,4-dimethyl-6-(3¹-hydroxyphenyl) analogs give not only 6-(4¹-bromo-3¹-hydroxyphenyl) derivatives but also dibrominated products in which a bromine atom has been substituted at a position *ortho* (6¹-) to the dihydrodiazepinium ring (86LA1380).

Not only do substituents at the 5- and 7-positions inhibit reactions at the *p*-position of a 6-phenyl substituent, but reactions may also be retarded or inhibited by substituents at the 1-4-positions. Thus a methyl group at the 2-position decreases the rate by a factor of 4, while two methyl groups

at this position decrease the rate 16-fold, despite these substituents being separated by seven atoms from the site of reaction (89LA133). This effect is the same as that observed in the case of substitution at the 6-position of the dihydrodiazepinium ring (see Section VI,C) and presumably has the same cause, possibly that initial attack by bromine occurs at the nitrogen atoms.

In keeping with this interpretation, introduction of one, or two, methyl groups at the 1- and 4-positions lowers the rates of bromination at the *p*-position of a 6-phenyl substituent by factors of 20 and 50, respectively (89LA133).

1,4,6-Triphenyldihydrodiazepinium perchlorate also does not react with bromine, although in this case there is the added factor that ¹³C-NMR spectra indicate lowered electron density in the phenyl rings, the electrons now being shared over three aryl rings [81JCS(P1)726]. The 1,6-diphenyl and 1,4-dibenzyl-6-phenyl analogs also do not react; the 1,4-bis(*p*-methoxyphenyl)-6-phenyl derivative is brominated (in the 6-phenyl group) but the 6-(*p*-methoxyphenyl)-1,4-diphenyl derivative is not [81JCS(P1)726].

6-Phenyl- and 2-methyl-6-phenyldihydrodiazepinium salts are halogenated at the *p*-position of the phenyl groups by *N*-bromo- and *N*-iodosuccinimide but not by *N*-chlorosuccinimide, whereas the 1,4-dimethyl-6-phenyl derivative reacts only with the *N*-bromosuccinimide [81JCS(P1)726].

6-Phenyldihydrodiazepinium perchlorate may be converted into the 6-(*p*-nitrophenyl) derivative by cold dilute nitric acid [81JCS(P1)726]. The ease of nitration again emphasizes the electron-donating and activating character of a 6-dihydrodiazepinium substituent on a benzene ring. The action of cold dilute nitric acid on the 1-methyl-, 2-methyl-, and 1,4-dimethyl-6-phenyl analogs gives *p*-nitrobenzoic acid as the isolated product [81JCS(P1)726]. Nitration must precede hydrolysis and oxidation because the product is *p*- rather than *m*-nitrobenzoic acid and in any case benzoic acid would not be nitrated under these conditions.

When 6-phenyldihydrodiazepinium perchlorate is dissolved in concentrated sulfuric acid a deep blue solution results. Electron spin resonance (ESR) spectroscopy indicated that either radicals or radical ions were formed [81JCS(P1)726]. They appear to be fairly stable, for the ESR and electronic spectra show little change after 24 h. The original salt can be recovered from these solutions.

The 6-phenyldihydrodiazepinium cation can be methylated on both nitrogen atoms by iodomethane and potassium carbonate in dimethylformamide. The 6-(*p*-hydroxyphenyl) analog is first methylated on both of the nitrogen atoms and only thereafter on the hydroxy group (86LA1387).

VII. Reduction of 6-Nitrodihydrodiazepinium Salts; 6-Aminodihydrodiazepinium Salts

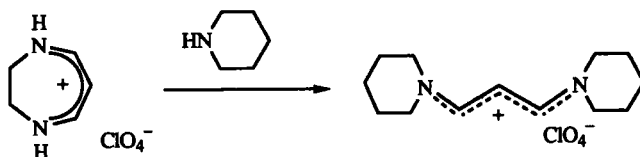
Nitro substituents in dihydrodiazepinium salts can be reduced by means of iron and acetic acid without reduction of the dihydrodiazepinium ring; for example *p*-aminophenyl-substituted dihydrodiazepinium salts have been obtained in this way [70JCS(C)617]. Although 6-nitro groups can also be reduced by metal and acid, it is not a satisfactory method for the preparation of 6-aminodihydrodiazepinium salts since the products apparently form complexes with the metal. 6-Amino derivatives are most conveniently prepared by catalytic reduction of the related nitro compound using either cyclohexene and palladium-charcoal or hydrogen and palladium-charcoal [68CI(L)1160; 70JCS(C)617].

6-Aminodihydrodiazepinium salts are stable, but it has not proved possible to isolate the bases. The salts react readily with benzaldehydes to form stable anils that can be reduced to benzylamino derivatives by sodium borohydride; this reagent also does not react with the dihydrodiazepine ring [68CI(L)1160; 70JCS(C)617].

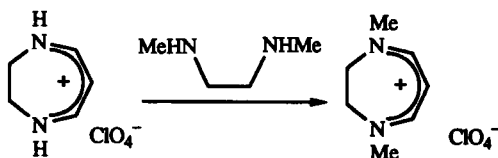
Reaction of 6-aminodihydrodiazepinium salts with sodium nitrite and acid produced stable solids with peaks in their IR spectra at 2200 cm^{-1} characteristic of aromatic and heteroaromatic diazonium salts [68CI(L)1160; 70CC1320, 70JCS(C)617]. These diazonium salts could be converted into 6-chlorodihydrodiazepines [68CI(L)1160; 70CC1320; 70JCS(C)617]. With alcohols or potassium iodide the diazonium group was replaced by a hydrogen atom; in the latter case it is likely that a 6-iodo compound was formed, which was then protodeiodinated in the acid conditions [74CI(L)525].

VIII. Reactions with Nucleophiles

The 5- and 7-positions of the dihydrodiazepine or dihydrodiazepinium rings are relatively electron-poor and thus are likely sites for nucleophilic attack. However 5,7-disubstituted derivatives are generally rather immune to the action of nucleophiles, presumably due to steric hindrance. 5,7-Unsubstituted derivatives react readily with amines. Thus piperidine converts the unsubstituted cation into an open-chain vinamidinium salt, displacing ethylenediamine [75JCS(P1)1260]. A similar reaction takes place with the 2,3-*cis*-diphenyl derivative, but the related base is not attacked by piperidine (83LA1230). By contrast the 5,7-dimethyl derivative was effectively unchanged after being kept in a methanolic solution of piperidine for a week [75JCS(P1)1260].

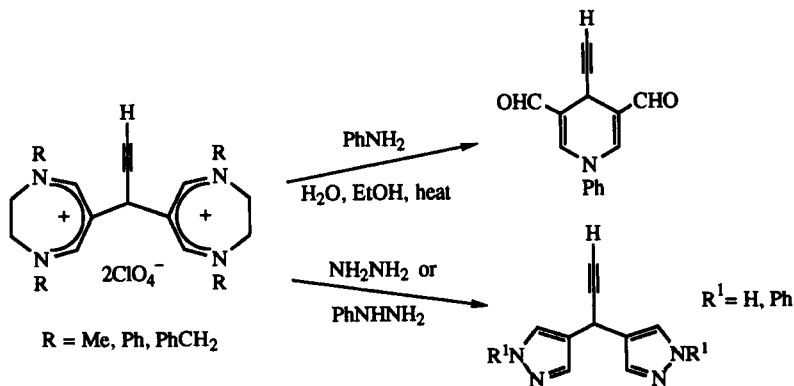


In some cases 1,2-diamines react in transdiazepination reactions; for example, the unsubstituted cation reacts with *N,N'*-dimethylethylenediamine to give a 1,4-dimethyldihydrodiazepinium salt:



6-Aryl derivatives react similarly with *N,N'*-dimethylethylenediamine [81JCS(P1)726]. Some 5-carboxy-7-(*o*-hydroxyphenyl)dihydrodiazepines have been shown to react with ethylenediamine or *N*-methylethylenediamine in the presence of potassium hydroxide with cleavage of the seven-membered ring (82MI1).

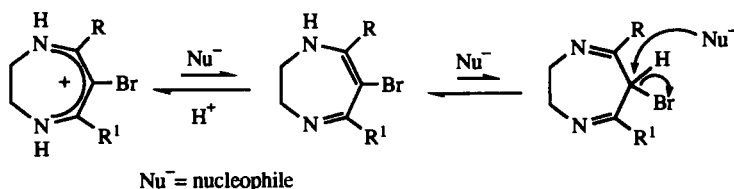
Many dihydrodiazepinium salts, and especially *N,N'*-disubstituted salts, are cleaved by strong aqueous alkali [60CB264; 66JCS(C)93; 81JCS(P1)726]. Other examples of nucleophilic attack at the 5,7-positions leading to opening of the dihydrodiazepine ring include the conversion of the 5,7-dimethyl derivative into *N,N'*-dibenzoylthylenediamine by shaking it with aqueous sodium hydroxide and benzoyl chloride [66JCS(C)780] and into acetylacetone bis(thiosemicarbazones) on treatment with thiosemicarbazides [67JCS(C)2400], and the reactions of a bisdihydrodiazepinium salt with aniline or hydrazines (77M929):



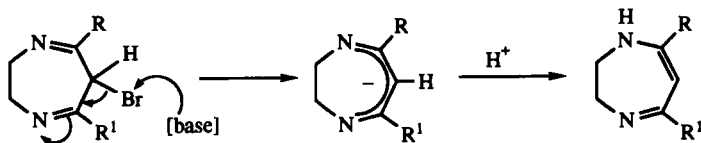
In each case the products formed are condensation products of the reactants with the bismalonaldehyde, which is derived by breakdown of the seven-membered rings.

It was mentioned in Section VI,C that 6-iododihydrodiazepinium salts may be prepared by reaction of their 6-bromo analogs with sodium iodide in methanol [69JCS(C)1449]. These 6-bromo compounds react similarly with methoxide ions to give the corresponding 6-methoxy derivatives [58JCS118; 69JCS(C)1449]. Other 6-alkoxy-, 6-aryloxy, and 6-amino derivatives have been prepared by nucleophilic substitution [69JCS(C)1449].

This ready nucleophilic substitution at the 6-position is surprising since this position is electron-rich in both dihydrodiazepines and dihydrodiazepinium salts and is the site at which electrophilic substitution occurs. The likely explanation is that in the presence of base some prototropic rearrangement of the normal dihydrodiazepine base into a bis-imino form takes place. Although the equilibrium concentration of the bis-imine is likely to be very small (it has not been observed spectroscopically) it would be strongly electrophilic at the 6-position owing to the combined effects of the bromine atom and the two azomethine groups, and could well be the reactive species in the nucleophilic substitution of the bromine atom:



In many cases reactions of 6-bromodihydrodiazepines with nucleophiles do not lead to the normal substitution products but instead the bromine atom is replaced by a hydrogen atom [69JCS(C)1449; 74CI(L)525]. It has been shown that protodebromination and nucleophilic substitution reactions are competing reactions rather than that nucleophilic substitution precedes the introduction of the hydrogen atom [69JCS(C)1449]. The dihydrodiazepines themselves may act as bases to bring about bromine-hydrogen exchange, for, when some bromodihydrodiazepines were heated in an inert solvent, slow replacement of the bromine by hydrogen was observed [69JCS(C)1449].



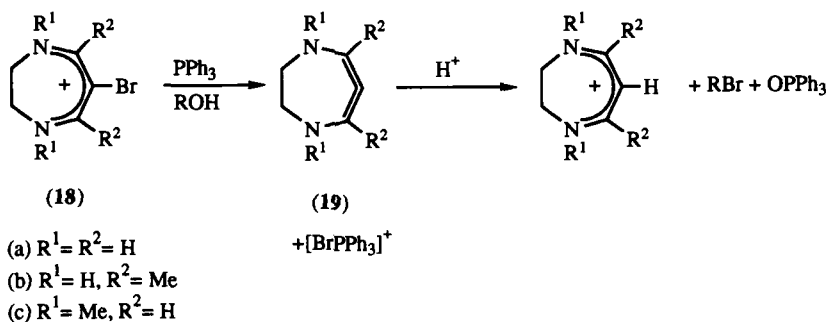
It seems likely that in this protodebromination the bisazomethine tautomer is again involved but that in this case nucleophilic attack takes place on the bromine atom, leading to a carbanion that is stabilized by delocalization of charge over the azomethine groups. This anion then extracts a proton from the solvent or from another diazepine molecule [69JCS(C)1449]. The involvement of this tautomer is particularly suggested by the fact that under identical conditions *N*-methylhydrodiazepines do not undergo this reaction.

The evidence available suggests that, in a general way, steric factors affect the course of the reaction. Increase in the size of the substituents at positions 5 or 7, or in the size of the nucleophile, appears to favor protodebromination over nucleophilic substitution. Furthermore it appears that 6-iododihydrodiazepines undergo protodeiodination rather than nucleophilic substitution irrespective of the size of the nucleophile or of the 5(7)-substituents, whereas 6-chlorodihydrodiazepines are less susceptible to protodehalogenation [74CI(L)525; 75JCS(P1)1260]. With thiourea, 6-bromo-5,7-dimethyldihydrodiazepine undergoes protodebromination whereas the 6-chloro analog forms a thiuronium salt, in contrast to the usually more ready formation of isothiuronium salts from bromo compounds than from chloro compounds [74CI(L)525]. It is reasonable that protodehalogenation should be favored for more bulky dihydrodiazepines or nucleophiles since this reaction has less steric demands than nucleophilic substitution. Similarly, both for steric reasons and because of the relative ease of formation of halonium cations, protodehalogenation should be favored with respect to nucleophilic substitution in the order iodine > bromine > chlorine. The equilibrium between the conjugated form of the dihydrodiazepine base and its bisazomethine tautomer may be somewhat more favorable to the latter if there are large 5(7)-substituents, since crowding between these substituents and the 6-substituents is thereby relieved.

In view of these findings it had been expected that the 6-bromo derivative of the otherwise unsubstituted dihydrodiazepinium salt, not yet obtained when the above studies were made, would undergo ready conversion into a 6-methoxy compound on treatment with methoxide ion. In fact the bromo compound was recovered unchanged after being heated with sodium methoxide in methanol for 30 min [75JCS(P1)1260]. Spectroscopic examination showed that throughout this time the only product formed was the corresponding 6-bromodihydrodiazepine base [75JCS(P1)1260]. As mentioned previously, if attack of nucleophiles on 6-halogeno compounds involves the bisazomethine tautomer, none the less this is present in only small amount; its formation is disfavored because of the loss of the conjugation of the vinamidine system, with its considerable stabilization

energy. However, there is some slight compensating energetic gain if there are large 5,7-substituents, since in the conjugated tautomer these substituents and the 6-halogen atom must be crowded, which leads to distortion of the bond lengths and bond angles, as has been shown by recent X-ray studies on the salts [90AX(C)1248; 91JCS(P2)1563], but this crowding is relieved when position 6 becomes tetrahedral in the bisazomethine tautomer. When no substituents are present at the 5,7-positions there will be no crowding in the conjugated form and hence no compensation in forming the bisazomethine tautomer. Hence there may be a vanishingly small contribution from this bisazomethine form, which would in turn explain the unreactivity of 6-bromodihydrodiazepine toward nucleophilic substitution [75C311, 75JCS(P1)1260]. Thus the surprising reactivity toward nucleophiles at position 6 is shown to be not an inherent property of the 2,3-dihydro-1,4-diazepine system but rather a consequence of a substituent effect.

Although salt **(18b)** reacts with methoxide ions in methanol or with amines by nucleophilic substitution, it reacts with triphenylphosphine or with isothiurea by protodebromination [81AG193, 81AG(E)190]. Since the pK_a for the acid-base equilibrium involving **(18b)** is 11.8 (64JCS2195), it seems unlikely that in the presence of triphenylphosphine in methanol there could be a sufficient amount of the bisazomethine base form present to sustain the protodebromination reaction proceeding via this base as intermediate. An alternative mechanism, in keeping with the known reactivity of triphenylphosphine toward bromine (74CSR87), could involve the following sequence of reactions:



MNDO calculations suggest that, for an isolated molecule, a structure involving an allenic system is energetically preferred to alternative possible valence isomers, and that there is appreciable separation of charge within the diaminoallenic system with net negative charges at positions 1,4, and 6 and net positive charges at positions 5 and 7, as in a dihydrodiazepine or its cation [82JCR(S)80].

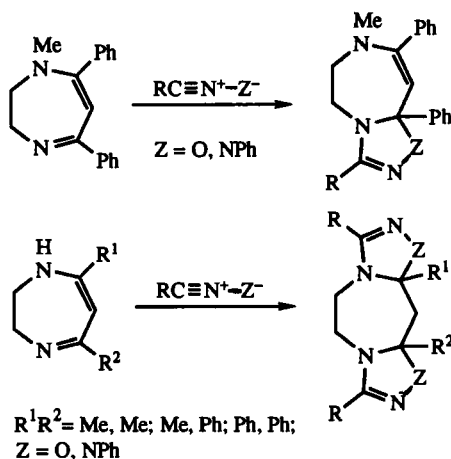
Similarly the cation (**18a**), which does not react with alkoxides [75JCS(P1)1260], is protodebrominated by triphenylphosphine, albeit a higher boiling solvent, pentan-1-ol, is required to promote the reaction. The salt (**18c**), which cannot form a dihydrodiazepine base, also undergoes protodebromination when heated with triphenylphosphine in pentan-1-ol [81AG193, 81AG(E)190].

These latter two examples add support to the projected mechanism. Other supporting features are that use of perdeuteriomethanol as a solvent for the reaction of (**18b**) provides the corresponding 6-deuteriodihydrodiazepinium salt and that in the protodebromination of (**18b**) in propan-1-ol, the other expected products, triphenylphosphine oxide and 1-bromopropane, were both isolated and characterized [81AG193, 81AG(E)190].

It is likely that the intermediate allene is protonated by the solvent when reaction takes place in an alcohol. In an aprotic solvent an allene generated from a salt lacking 1,4-substituents could well be protonated by transfer of a proton from a nitrogen atom but, if both nitrogen atoms bore alkyl substituents, such a process is ruled out. In accord with this, treatment of salt (**18b**) with triphenylphosphine in dry ethyl benzoate as solvent provided the expected protodebrominated product, but similar treatment of (**18c**) provided only polymeric material, presumably resulting from alternative reactions of the intermediate species [81AG193, 81AG(E)190].

IX. Cyclo-addition Reactions

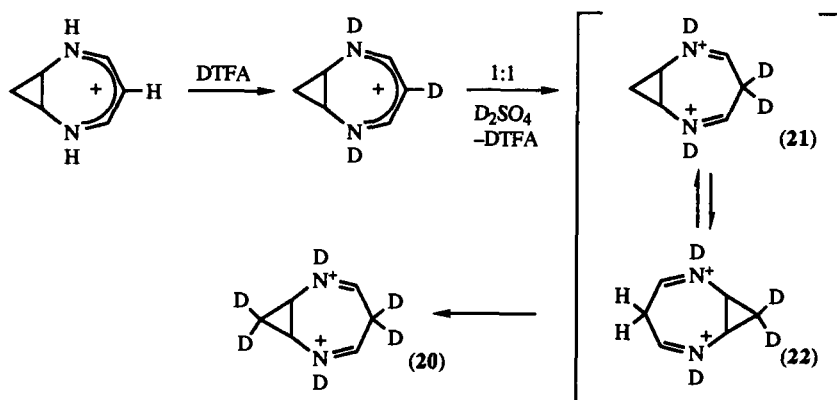
Dihydrodiazepines have been shown to undergo regioselective cyclo-addition reactions with nitrile oxides or nitrile imines (88MI1; 89JHC1619).



X. Rearrangement Reactions

The use of Cope rearrangements in the preparation of dihydrodiazepines has been mentioned in Section II.

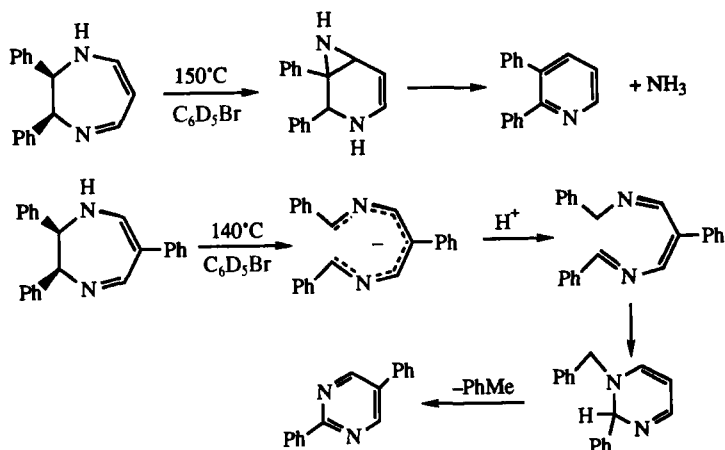
An interesting example of a degenerate Cope rearrangement involving a dihydrodiazepinium salt has been reported [77AG668, 77AG(E)643]. When a 2,3-cyclopropanodihydrodiazepinium salt was dissolved in deuteriotrifluoroacetic acid, deuterium exchange of the 1,4,6-hydrogen atoms occurred at once. On addition of deuteriosulfuric acid to the solution the hydrogen atoms of the cyclopropane ring were also replaced and a hexadeuteriodication (**20**) was formed:



Formation of the dication (**21**) provides a species which undergoes a Cope rearrangement to form (**22**), which is then further deuteriated, giving rise to the observed hexadeuteriated product (**20**). If trifluoromethylsulfonic acid is used, protonated species analogs to (**21**) and (**22**) are formed and the rearrangement reaction is detectable by 1H -NMR spectroscopy. At room temperature the cyclopropane signals appear as a ABX_2 system but when the temperature is raised, the structure of this system disappears. At $\sim 110^\circ C$ the signals for the 2,3- and 5,7-hydrogen atoms coalesce. The ΔG^\ddagger value for the rearrangement is $73 \pm 2 \text{ kJ mol}^{-1}$. Methyl groups substituted at the 5,7-position would be expected to hinder such a Cope rearrangement and this is found to be so, reaction being much slower. In this case, in order to obtain the hexadeuterio derivative, it is necessary to heat a solution of the salt in deuteriotrifluoromethylsulfonic acid [77AG668, 77AG(E)643].

Another type of rearrangement, involving ring-contraction of the seven-membered ring, occurs when *cis*-2,3-diphenyldihydrodiazepine is heated above its melting point; 2,3-diphenylpyridine and ammonia are formed

(77TL2709; 83LA1230). In contrast, *cis*-2,3,6-triphenyldihydrodiazepine is converted into 2,5-diphenylpyrimidine. The suggested mechanisms are as follows (83LA1230):



It was noted in Section V,D that similar breakdowns involving ring-contraction sometimes take place in the mass spectrometer (77AJC365).

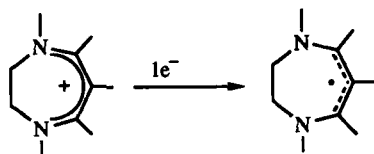
XI. Electrochemical Studies

The first reported electrochemical study on dihydrodiazepines was a potentiometric determination carried out on the 5,7-dimethyl derivative, which provided a pK_a between 13 and 14 for the base-monocation system (40HCA1162).

Studies of the electrochemical reduction of a variety of dihydrodiazepinium salts, in aqueous ethanol (UP4) or in *N,N*-dimethylformamide [71JCS-(B)1615; 78CC499; 79BSB113; 80JCS(P2)668, 80JCS(P2)1441; 81JCS-(P2)801], show that they undergo one-electron reduction processes that take place in the range -0.9 to -1.5 V. Dihydrodiazepine bases are inactive to about -2.1 V, at which point two-electron processes appear [80JCS(P2)668].

In the case of 5,7-disubstituted dihydrodiazepinium salts, this first reduction is reversible and may be followed by a second one-electron reduction at ~ -2.0 V [71JCS(B)1615; 80JCS(P2)668].

The first step involves the formation of a allyl radical.



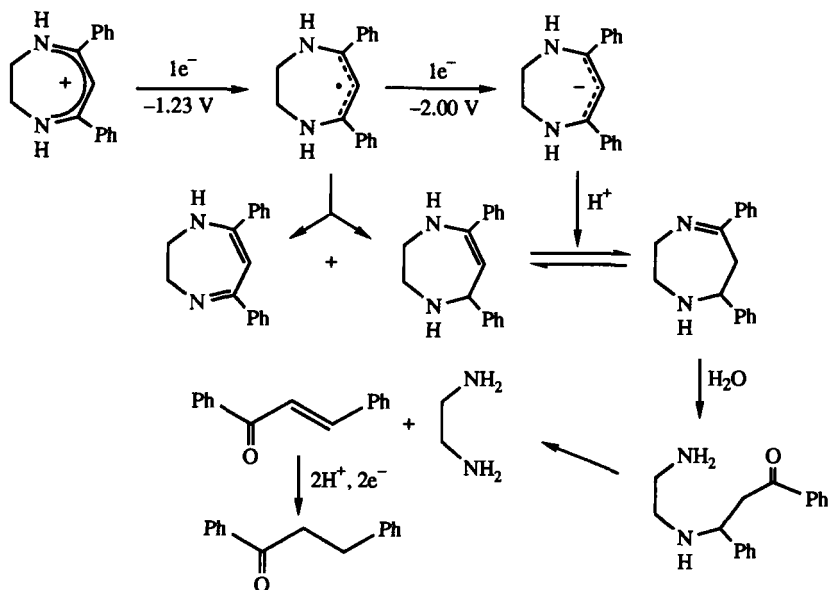
Reactions subsequent to this initial reduction involve the termini of this allyl system, i.e., the 5- and 7-positions. If, however, there are substituents at the 5,7-positions they inhibit or retard further reactions, and the initial reduction is reversible:



In the case of 5,7-unsubstituted compounds, reduction is followed immediately by a chemical reaction, preventing the setting-up of an equilibrium between the cation and the radical, and causing the reduction to be effectively irreversible:



Preparative studies on the 5,7-diphenyl derivative suggest that reduction is followed by a disproportionation process leading to the formation of the dihydrodiazepine base and a tetrahydrodiazepine [UP4; 80JCS(P2)668].

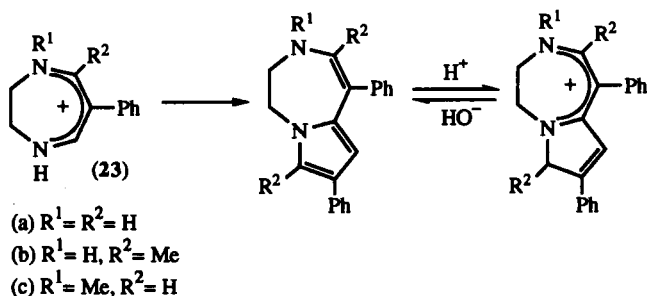


The isolated products were the 5,7-diphenyldihydrodiazepine base (50%), together with ethylenediamine, benzylidenacetophenone, and benzylacetophenone. 5,7-Diphenyldiazepinium perchlorate is more readily

reduced than its 5,7-dimethyl analog (-1.631 V) [71JCS(B)1615; UP5] presumably reflecting the lower stability of the alkyl radical formed in the latter case; the diphenyl radical gains some stabilization from its terminal phenyl substituents.

If no substituents block the very reactive 5,7-positions in the allyl radicals, other reactions may readily ensue at these sites. Reduction of 1,4-diphenyldihydrodiazepinium perchlorate in aqueous ethanol led to the formation of 1,4-diphenylhexahydrodiazepine and 1,4-dianilinoethane (UP4), but reductions of a number of phenyl-substituted dihydrodiazepinium salts in *N,N*-dimethylformamide provided unexpected products arising from further reactions undergone by the initial reduction products [78CC499; 79BSB113; 80JCS(P2)1441; 81JCS(P2)801].

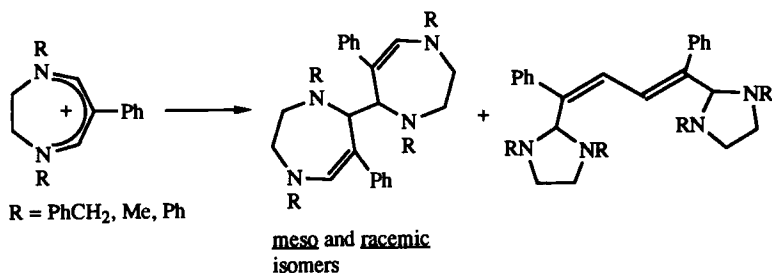
The products isolated from the reduction of the salts (23) were pyrrolodiazepines [78CC499; 80JCS(P2)1441].



In the case of (23a) the yield of isolated product astonishingly exceeds 90%. A logical route for the formation of these products involves dimerization of the initially formed radicals at their 7-positions to give bis(tetrahydrodiazepinyl) derivatives, followed by attack of the NH group of one ring onto the 5-position of the other ring, accompanied by extrusion of ethylenediamine (or its *N*-methyl derivative) from this second ring [80JCS(P2)1441].

The structure of the pyrrolodiazepine has been confirmed by X-ray crystallography, as has that of the pyrrolodihydrodiazepinium salt, which is formed in acid [78CC499; 80JCS(P2)1441]; this latter reaction has been discussed more fully in Section III,A.

Dimeric products, whose structures have been confirmed by X-ray crystallography [79BSB113; 80AX(B)1418], have also been isolated from the electrochemical reduction of *N,N'*-disubstituted 6-phenyldihydrodiazepinium salts [79BSB113; 81JCS(P2)801]. In these cases formation of pyrrol-



lodiazepines is not possible because both nitrogen atoms carry substituents. The products were hydrolyzed by concentrated hydrochloric acid to give the corresponding N,N'-disubstituted ethylenediamine dihydrochlorides; in the case of the tetra-*N*-benzyl-di-imidazolidinylbutadiene, 2,5-diphenylhexa-2,4-diene-1,6-dial was also isolated [81JCS(P2)801]. Cyclic voltammetry experiments on the bis(tetrahydrodiazepinyls) indicated that they could be oxidized to bis(dihydrodiazepinium) salts, which could be reduced again to the bis(tetrahydrodiazepinyls) [81JCS(P2)801]. Studies of the isolated products (R = PhCH₂) showed that the *meso*-bis(tetrahydrodiazepinyl) could be converted into its racemic isomer, which in turn can be converted into the butadiene derivative. The *meso*-racemate interchange is effected by heating the *meso* isomer in dimethylformamide at 100°C. Solution of the racemate in a cold mixture of chloroform and ethanol provides, as the solvents evaporate, a quantitative yield of the butadiene. The mixture of solvents is necessary; the racemate remains unchanged in chloroform and may be recrystallized from hot ethanol with only a trace of rearrangement product being formed.

Perhaps the most consistently satisfying and enjoyable feature of the chemistry of 2,3-dihydro-1,4-diazepines and 2,3-dihydro-1,4-diazepinium salts has been their ability to provide, quite consistently, unexpected results and products. There is every hope that these compounds will continue to maintain this tradition and provide interesting new facets in their chemistry in the future.

ACKNOWLEDGMENTS

We thank Dr. D. R. Marshall (University College of North Wales) for constructive help in compiling this review and for his general contributions to our understanding of 2,3-dihydro-1,4-diazepines and their salts; we have in places unashamedly plagiarized his words, and conversations over the years have contributed much to the review. We also thank Dr. S. Mesher for Chem Drawing the formulae.

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Ring Transformations of Five-Membered Heterocycles*

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* Dedicated to the memory of Professor Michele Ruccia.

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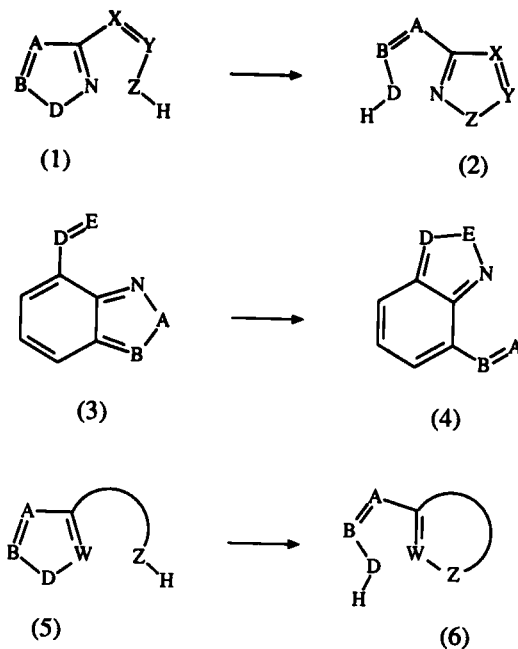
I. Introduction

SCOPE AND ORGANIZATION

Ring transformations of heterocycles constitute an interesting area that continues to be of great importance in mechanistic studies and in synthetic design. An extensive literature exists, and an increasing number of publications continue to appear. A comprehensive treatment of "Ring Transformations of Heterocycles" appeared in 1973 (73MI1, 73MI2), and many other reports have been published in monographs. Moreover, many reaction types have been surveyed in "Comprehensive Heterocyclic Chemistry" (84MI1), and specific categories also have been reviewed. With reference to five-membered heterocycles, an enormous variety of ring transformations are known, and there has always been some difficulty in rationalizing these reactions systematically. A greatly significant classification can be recognized in molecular rearrangements of heteromonocycles, which involve the participation of a given number of side-chain atoms in the new ring formation, including special rearrangements where interchanges of annular atoms simply occur (84JHC627).

Regarding molecular rearrangements involving the participation of a three-atoms side-chain, the conversion of **1** \rightarrow **2** represents the generally accepted Boulton–Katritzky scheme [67JCS(C)2005] that has a ring-conjugated side-chain reacting as a nucleophile toward the pivotal annular nitrogen. This class of rearrangements, which covers many azole-to-azole conversions, has already been reviewed as mononuclear heterocyclic rearrangements (81AHC141). The scope and some restrictions have been pointed out (74MI1; 81AHC141; 86JST215). For benzo-fused systems, the corresponding general pattern **3** \rightarrow **4** has also been considered [64AG(E)693; 66JCS(B)1004], and many such rearrangements have been systematized (69AHC1; 74MI1; 78HCA2628; 79MI1; 80JOC1653; 81AHC1, 81AHC251; 90DOK1127).

This review is concerned with rearrangements of five-membered heterocycles represented by the generalized pattern **5** \rightarrow **6**, where the W pivotal center is a nitrogen (W = N), sulfur (W = S), or carbon atom (W = C),



SCHEME 1

and the side-chain contains three or four participating atoms. Here, one encounters a large variety of rearrangements of five-membered heterocycles into five- or six-membered ones. The extension of the Boulton-Katritzky scheme to substrates containing a sulfur [74MI1; 84JHC627] or a carbon atom [76JCS(P1)315] as the pivotal center is now known. The object of this work will be to provide a comprehensive systematization of these reactions widely distributed in the literature.

At least formally, the rearrangement proceeds by the nucleophilic attack of the Z atom on the pivotal center W, with a concerted (or subsequent) breaking of the D—W bond in an S_Ni -type reaction. On the other hand, when the side-chain is a ring-conjugated allyl moiety containing 4π -electrons, the rearrangement can be viewed as a 6π -assisted heteroelectrocyclic reaction [71BSF1925; 79CRV181; 80AG(E)947] into a bicyclic species (as intermediate or transition state), with subsequent or concerted cleavage of the D—W bond; this latter step, in its turn, could be also considered as a retro-electrocyclic reaction. Moreover, when $W = S$, thiapentalene-type intermediates or reversible bond-switches at the hypervalent sulfur have been also pictured. Furthermore, a thermally or photoinduced ring-opening (or fragmentation) of the starting heterocycle could precede the new ring closure, which therefore implies a heterocyclization

of an open-chain species engaging the side group. In this general pattern one could also include ring-opening by the action of an external nucleophilic species.

Since the current literature does not appropriately index heterocyclic rearrangements, some effort has been devoted to present an update covering about 1970 until the end of 1990, referring to the already mentioned work (73MI1) for the previous reports; those special cases that are considered characteristic of a typical reactivity will however be reviewed again. Rearrangements involving the nitrogen atom as the pivotal center have been reviewed in this series (81AHC141) and will be updated from that time. The material will be organized in three sections, following a subdivision based on the pivotal center in the rearranging ring, namely, a nitrogen, sulfur, or carbon atom, respectively. Aromatic substrates will be emphasized and dihydro or tetrahydro species will be mentioned only when they represent behavior of particular interest. As for the terminology, the term isoheterocyclic or ring-degenerate will indicate rearrangements furnishing the same ring system, whereas the fully degenerate type will have starting and final products exactly identical.

II. Rearrangements Involving the Pivotal Nitrogen Atom in the Starting Ring

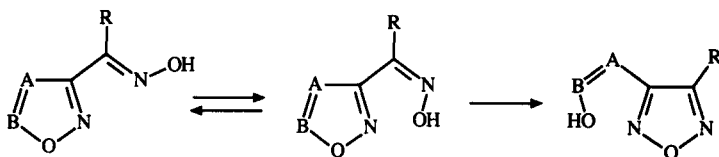
Since the appearance of the review "Mononuclear Heterocyclic Rearrangements" (81AHC141), many more reports have been published. These reactions have been studied with a more systematic approach, particularly when mechanistic studies and structural aspects of the starting heterocycle and the side-chain are concerned. Moreover, there are many applications in heterocyclic synthesis. We now intend to present an update of this field, pointing out some new aspects: mechanistic studies, photochemical approaches, and the influence of the side-chain geometry on the rearrangement. Apart from these general aspects, we shall show, at first, new examples of rearrangements of the type $1 \rightarrow 2$ ($D = O$) in which an $O-N$ bond is cleaved, maintaining, for convenience, the previous model. For a given sequence XYZ, the results will be presented in order of decreasing reactivity, 1,2,4-oxadiazole, isoxazole, 1,2,5-oxadiazole, quoting the heterocycle only when new examples are discussed. The results of photochemical (II,A,10) and mechanistic studies (II,B) will be presented in special sections. Rearrangements involving the cleavage of an $N-N$ bond will be discussed separately (Section II,C).

A. REARRANGEMENTS INVOLVING CLEAVAGE OF AN O—N BOND

1. *Rearrangements Involving a Side-Chain CNO*

Rearrangements involving the side-chain CNO of an oxime group have been known for long time and widely used as a synthetic tool for 1,2,5-oxadiazole (furazan) derivatives (Scheme 2) (81AHC141). A recent and significant article considers this specific topic (90CHE1199). Up to the time of the previous review, systematic studies concerning the influence of oxime geometry on the rearrangement have not been reported. Recently, this problem has been discussed in some papers, and in some instances some discrepancies in the literature have been corrected.

As previously claimed (81AHC141), the general scheme of heterocyclic rearrangements $1 \rightarrow 2$ presupposes a Z-shaped geometry of the side-chain



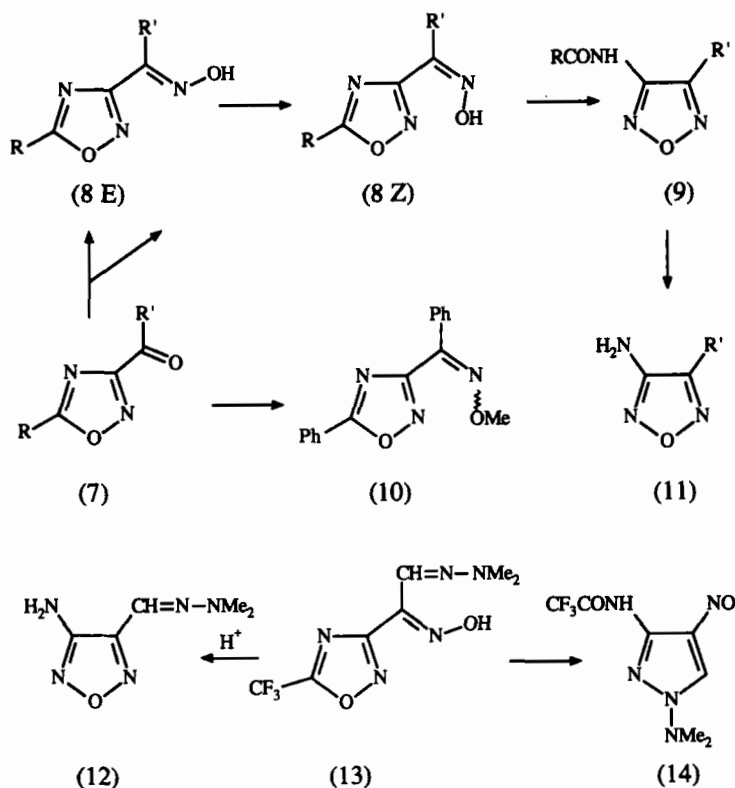
SCHEME 2

with respect to the reacting heterocycle. (Since there is a variable priority order between groups linked to the X atom of the side-chain, in order to keep a uniform *E* and *Z* notation for geometrical isomers, we will always assign the higher priority to the rearranging heterocycle.) Therefore, when the side-chain has an *E* geometry, the rearrangement will proceed only under those experimental conditions that enable isomerization to the *Z* form. This last consideration seems particularly remarkable for an oxime. In fact, although the rearrangement reactions go much more easily when there is an anionic sequence XYZ, which enhances the nucleophilicity of the terminal atom, the configurational isomerization in the oximate anion is very slow [77JA5382; 79JCS(P2)1437]. In the light of this new approach, in some instances, the unsuccessful rearrangement of a 3-acylazole oxime into the corresponding furazan has been considered as an indication of an *E* geometry of the oxime group. A dependence on the geometry of the oxime is also reported in the base-induced rearrangement of 3-acylpyridinium oxime iodides into isoxazole derivatives (80CPB2083) (Section IV,4). On the other hand, a similar dependence is observed in the base-induced ring closure of ortho-halogenophenyl ketone oximes into 1,2-benzisoxazoles (77JHC793).

a. *1,2,4-Oxadiazole*. The literature [85JCR(M)2184, 85JCR(S)190, 85JHC97; 90CHE1199] reports a critical examination of the oximation of some 3-acyloxadiazoles, and of the rearrangement of the corresponding oximes as function of the geometry of the oxime group itself. A comprehensive treatment of this topic follows.

The reaction of the 3-benzoyl-1,2,4-oxadiazoles **7** ($R = \text{Ph}, \text{Me}, \text{H}, \text{NH}_2$; $R' = \text{Ph}$), with hydroxylamine as the hydrochloride or as the free base, results in a mixture of *E* oximes **8E** and rearranged furazans **9**. These latter arises from a spontaneous rearrangement of unisolated oximes **8Z**. This behavior is due to the great sensitivity of the 1,2,4-oxadiazole heterocycle toward rearrangement. Therefore, the oximation could actually involve the initial formation of both *E* and *Z* oximes, also proved by the isolation of both *E* and *Z* O-methyloximes **10** (85JHC97). These results allowed correction of some discrepancies in the literature. In fact, in the oximation of the 3-benzoyloxadiazole **7** ($R = \text{H}$; $R' = \text{Ph}$) only the corresponding formylfurazan **9** had been reported as the reaction product (58G463). Moreover, in the oximation of the 3-benzoyl-5-aminooxadiazole (**7**; $R = \text{NH}_2$; $R' = \text{Ph}$), only the corresponding oxime (configuration not stated) had been described (73JHC357). In this case it was verified that the product described as an oxime really was the rearranged oxadiazole **9** ($R = \text{NH}_2$; $R' = \text{Ph}$) [85JCR(M)2184, 85JCR(S)190]. As expected, the oximation of the 3-acetyloxadiazole **7** ($R = \text{Ph}$; $R' = \text{Me}$) gives the *E* oxime only. Generally, in the formation of acyclic ketoxime isomers $R(\text{Me})\text{C}=\text{N}-\text{OH}$, the more bulky is R , the more predominant is the isomer bearing Me and OH *cis* (63JA2326; 74RTC300; 75OMR524). In the presence of bases this oxime remains unchanged, thus supporting its configuration. However, the rearrangement into the corresponding acylaminofurazan **9** occurs on melting (Scheme 3) (31G138).

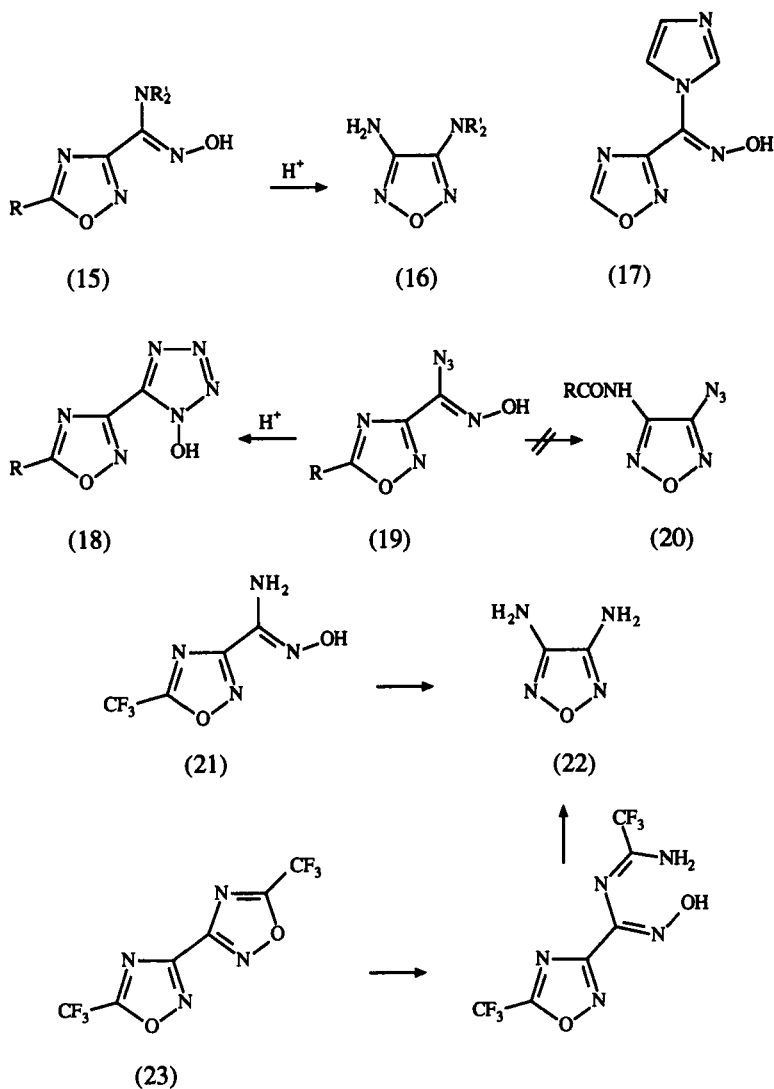
On the basis of these findings, oximes of 3-acyl-1,2,4-oxadiazoles must exist as *E* isomers only, and their rearrangement into furazans must take place only under those experimental conditions that favor the *E*-to-*Z* isomerization process. The absence of a rearrangement in basic media is explained by the slow configurational isomerization in the oximate anion; on the other hand, the thermally induced rearrangement into acylaminofurazans (**9**) and, in some instances, the acid-induced rearrangement into the corresponding 3-aminofurazans (**11**) are the result of a preliminary *E*-to-*Z* isomerization (thermally induced or acid induced) followed by a spontaneous rearrangement, and then by hydrolysis of the acylamino group. For the hydrazone-oxime **13**, where two types of sequences can be recognized, acid catalysis produces the aminofurazan **12** as a result of a rearrangement involving the oxime sequence. In the absence of acid catalyst, the unfavorable oxime geometry leads to the rearrangement involving the hydrazone



SCHEME 3

moiety, resulting in the formation of nitrosopyrazole **14** (Scheme 3) (90CHE1199).

Regarding the oxadiazolyl-amidoximes, some considerations on the isomerization-rearrangement process are reported as a function of the structure of the amidoxine group, which influences the geometrical isomerization barrier (90CHE1199). For N,N-disubstituted amidoximes **15** (R = H, CF₃; NR'₂ = pyrrolidinyl, piperidyl), acid treatment induces the isomerization of the oxime group, which is followed by spontaneous rearrangement, and then by hydrolysis to aminofurazans **16** (90CHE1199; 91URP1599372). Exploiting this reactivity, a generalized method for obtaining 3-amino-4-alkylaminofurazans, employs the reaction of 5-trifluoromethyl-3-carbohydroxamic acid halide with primary or secondary amines, followed by the isomerization-rearrangement of the resulting amidoximes (91URP1599372). On the other hand, the imidazolyl-oxime **17** does not isomerize on acid treatment, and does not rearrange



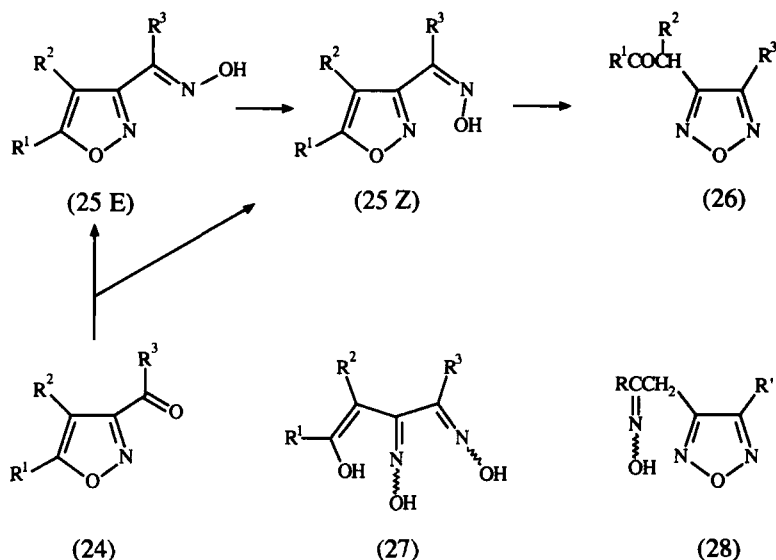
SCHEME 4

(90CHE1199). Hydrogen chloride treatment of azidooximes **19** ($R = H$, CF_3) is claimed to induce isomerization followed by the ring closure into the *N*-hydroxytetrazole **18**, and not the expected rearrangement into azidofurazans **20** (Scheme 4) (89CHE1419).

By reacting with ammonia, the amidoxime **21** rearranges into 3,4-diaminofurazan (**22**) (88CHE707). The same diaminofurazan **22** is also reached

by similarly reacting the dioxadiazole **23**. Here, an opening of one of the oxadiazole rings, followed by isomerization of the oxime group with consequent rearrangement and, finally, by hydrolysis of the resulting side-chains, is suggested (Scheme 4). Apart from the ring opening in compound **23**, the rearrangement would proceed by the typical mechanism, for which the presence of open-chain intermediates is not imperative. As regards the configurational isomerization of an oxime, in contrast to ketoximes or *N,N*-disubstituted amidoximes, unsubstituted amidoximes and the *N*-monosubstituted ones isomerize even in the presence of a base [79JCS(P2)1437; 90CHE1199].

b. *Isoxazole*. The literature also reports a critical review of the oximation reaction of 3-acylisoxazoles, and of the rearrangements of the corresponding oximes as a function of their geometry [83JCS(P1)483; 90CHE1199]. The oximation of 3-benzoylisoxazoles **24** ($R^1 = R^3 = \text{Ph}$, $R^2 = \text{H}$; or $R^1 = R^2 = R^3 = \text{Ph}$; or $R^1 = \text{Me}$, $R^2 = \text{H}$, $R^3 = \text{Ph}$) with hydroxylamine hydrochloride leads to a mixture of *E* and *Z* oximes **25** (*R* the same), without formation of the rearranged furazans [83JCS(P1)483], thus pointing out the lower reactivity of the isoxazole compared with that of the 1,2,4-oxadiazole (Scheme 5). This result allows a correction of the literature, according to which (a) the oximation of **24** ($R^1 = R^3 = \text{Ph}$,



SCHEME 5

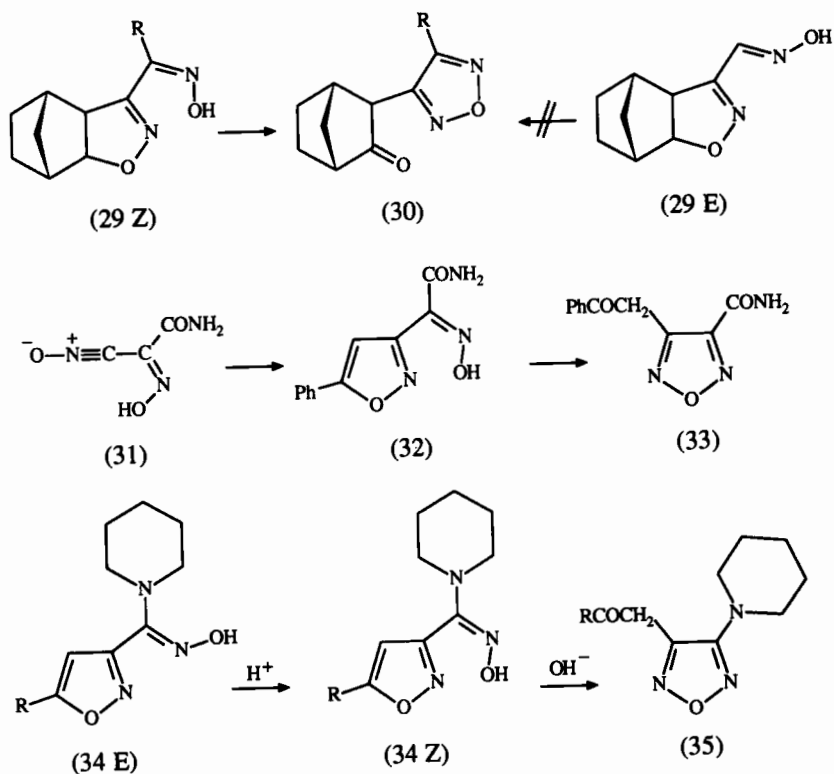
$R^2 = H$) gives a mixture containing an oxime (configuration not stated) and the rearranged furazan (37G779) and (b) the oximation of **24** ($R^1 = R^2 = R^3 = Ph$) results in the rearranged furazan only (37G55; 48G630). In this context, it has been proved that these presumed 1,2,5-oxadiazoles really are the *E* and *Z* oximes, respectively. As for the base-promoted rearrangement, only the *Z* oximes easily rearrange into the furazans. By contrast, the *E* oximes remain unchanged when treated with aqueous potassium hydroxide [83JCS(P1)483].

As expected, oximation of 3-acetylisoaxazoles **24** ($R^1 = Me, Ph$; $R^2 = H$; $R^3 = Me$) leads only to a single isomer that must be regarded as *E*. Because of this configuration, these oximes do not rearrange when treated with bases. The role of open-chain intermediates of type **27** in the rearrangement (38G792) can be questioned. In fact, only the *Z* oximes undergo a rearrangement in the presence of either aqueous bases or bases in dipolar aprotic solvents, whereas the *E* oximes remain unchanged when treated under the same experimental conditions [83JCS(P1)483]. Isolation of furazan oximes **28** in the oximation of some 3-acylisoaxazoles is explained by the work-up procedure, such as the use of an excess of reagent and/or basification before.

The influence of the oxime geometry on the base-promoted rearrangement is pointed out for compounds **29** (85T5181). Thus, when treated with aqueous potassium hydroxide at room temperature, *Z* isomers **29Z** ($R = H$, *E*-oxyiminomethyl), arising as cycloadducts of the dimer or trimer of fulminic acid and norbornene, rearrange into **30**. On the contrary, the *E* isomer **29E** remains unchanged under similar conditions of aqueous bases (Scheme 6).

Nitrile oxide **31**, arising from the thermolysis of the furoxan-dicarboxamide in refluxing xylene/DMF, reacts with phenylacetylene leading to the furazan **33** directly, via the unisolated isoxazole *Z* oxime **32** where the geometry of the starting furoxane and nitrile oxide is maintained (85T727). Analogously, thermolysis of the furoxan-dicarboxamide in the presence of olefines produces 3-carbamoyl-4(2-hydroxy)ethylfurazans as the rearrangement products of the initially formed Δ^2 -isoxazoline oximes in the correct configuration (85T727). As already observed for the 1,2,4-oxadiazole system, also for isoxazole amidoximes there are reports on the behavior of the geometrical isomers toward the isomerization-rearrangement process (90CHE1199). In the presence of acid, the *E* *N,N*-disubstituted amidoximes **34E** ($R = H, Ph$) isomerize into the *Z* isomers (**34Z**), which, in turn, rearrange into **35** on reacting with bases [(Scheme 6); for the *E* and *Z* notation, see p. 53].

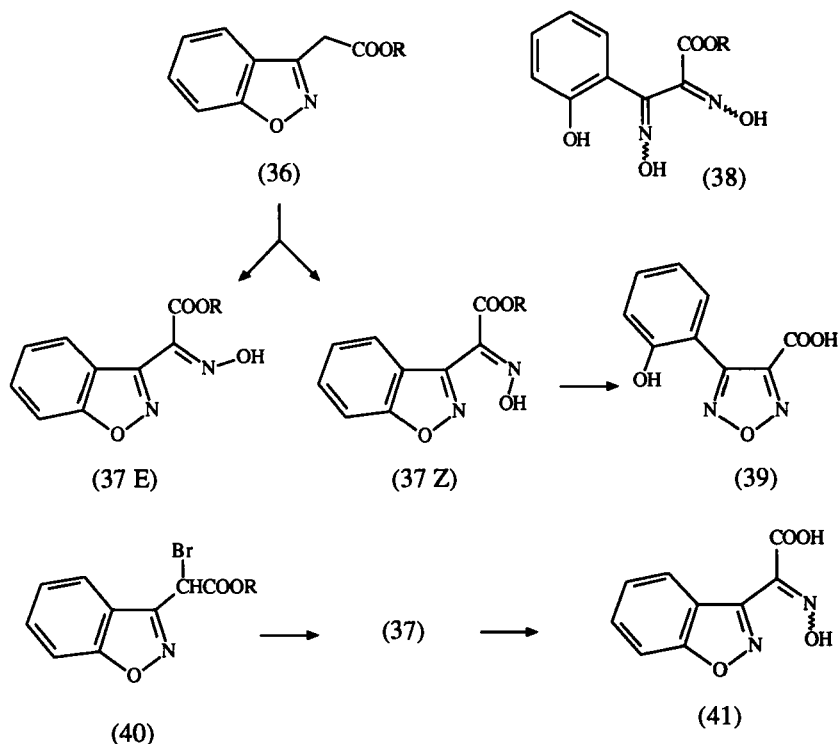
The literature (83JHC385) reports that nitrosation of benzisoxazoles **36** with isoamyl nitrite and sodium methoxyde results in a mixture of **37Z**



SCHEME 6

and rearranged furazan carboxylic acid **39**, this latter being the main product. Formation of the oxadiazole is explained by assuming a rearrangement involving open-chain intermediates **38**. The reaction between the α -bromoester **40** and sodium nitrite in methanol, in addition to the corresponding α -hydroxyester as the main product, gives a mixture of both oxime isomers (**37**), from which, on hydrochloric acid treatment, a mixture of both hydroxyiminocarboxylic acid isomers **41** results. From this latter mixture, on reacting with 2 *N* sodium hydroxide at room temperature, rearranged **39** arises (Scheme 7) (83JHC385).

Our opinion is that the actual configuration of oximes **37** should be inverted. Nitrosation of **36** in the presence of an alcoholate should result in the two *E* and *Z* oximes; the *Z* isomer will suffer a spontaneous base-induced rearrangement into the furazan **39** and will not be isolated. Furthermore, the reported spectroscopic data agree with the inverted configuration. The intermediacy of open-chain species in the rearrangement

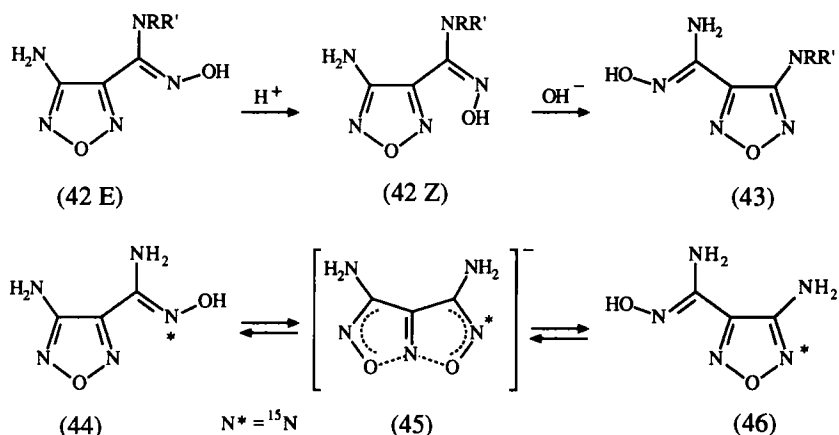


SCHEME 7

could be questioned, and a revision of these reactions as a function of the configuration of the oxime group could be appropriate.

c. *1,2,5-Oxadiazole*. A side-chain XYZ = CNO in a 1,2,5-oxadiazole system suggests the occurrence of an isoheterocyclic (ring-degenerate) rearrangement, which could be also of the fully degenerate type. An isoheterocyclic process is reported for amidoximes **42**. Thus, *E* *N,N*-disubstituted compounds **42E** [*R* = *R*' = Me; *R-R*' = (CH₂)₄, (CH₂)₅] undergo the expected acid-induced isomerization into geometrical isomers **42Z**, which, in turn, can be rearranged into furazans **43** under severe conditions such as treatment with bases at 120–140°C (Scheme 8). On the other hand, *E* *N*-monosubstituted amidoximes **42E** (*R* = H; *R*' = PhCH₂, isopropyl) can be even isomerized and then rearranged into the corresponding furazans on treatment with bases. Moreover, although in principle reversible, the reverse reaction has not yet been observed (90CHE1199; 91CHE102). By using mass spectroscopy, the fully degener-

ate rearrangement can be shown for the labeled amidoxime **44** (88CHE1410). After heating **44** at 130–140°C in the presence of potassium hydroxide, the mass spectrum of the resulting mixture shows the presence of equimolar amounts of **44** and **46**, thus suggesting the occurrence of the degenerate rearrangement (preceded and followed by configurational isomerization), likely through the anionic species **45** (Scheme 8).

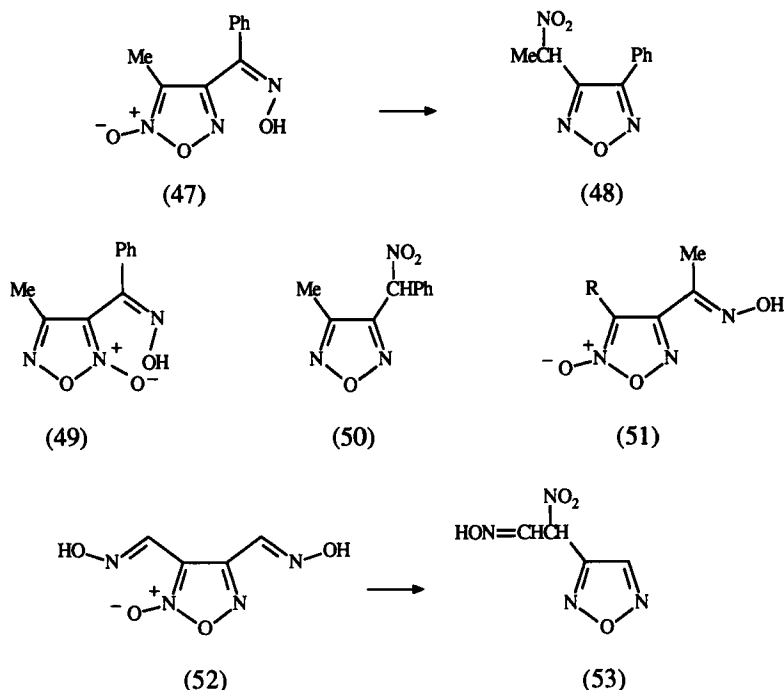


SCHEME 8

In the furoxan series, the rearrangement of the benzoylmethylfuroxan oxime **47** into the furazan **48** with bases at room temperature is reported (82G181), and the favorable *Z* geometry of the oxime group (68T395) is pointed out (Scheme 9). In describing this rearrangement, it is emphasized that for the benzoylmethylfuroxan oxime the literature erroneously reported the structure **49**, and for the corresponding rearrangement product the structure **50** had been erroneously considered (36G819). A related reaction could be the rearrangement of **52** into **53**, for which hydrolytic open-chain intermediates are suggested (75LA1029; 81AHC251). Acetylfuroxan oximes **51** ($R = Me, Ph$) do not rearrange on treatment with bases (37G388, 37G518), thus suggesting the unfavorable *E* geometry, supported by X-ray crystallography [87JCS(P2)523].

2. Rearrangements Involving a Side-Chain CNN

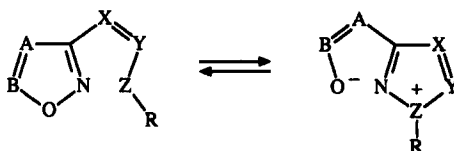
During the last few years, the reactivity of the widely studied (81AHC141) sequence $XYZ = CNN$ has been considered for some special aspects. Arylhydrazones of 3-benzoyl-1,2,4-oxadiazoles and 3-benzoyli-



SCHEME 9

soxazoles have been the substrates for mechanistic studies (Section II,B); moreover, for a hydrazone side-chain, the reactivity of a XYZ-R sequence, according to the Scheme 10 has been also pointed out.

a. *1,2,4-Oxadiazole*. Z N,N-disubstituted hydrazones **55Z** present a marked reactivity in the reaction involving nucleophilic attack on the ring nitrogen atom, and this behavior is ascribed to steric and/or electronic features connected with the N,N-disubstituted hydrazone moiety [82JCS(P)165; 85JHC97]. Thus, steric hindrance should minimize conjugation between the substituted nitrogen lone-pair and the imino group,

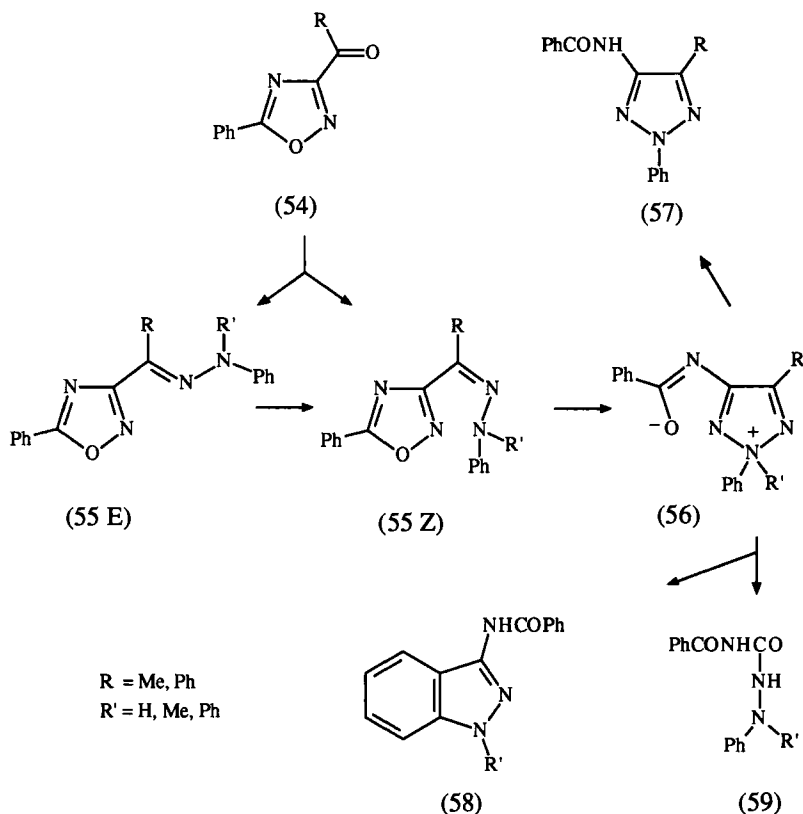


SCHEME 10

and therefore should favor interaction with the annular atom in new bond formation. Isolation of hydrazones **55Z** in the reaction between oxadiazolyl ketones **54** and the *N,N*-disubstituted hydrazine, as well as the evolution of the triazolium salt **56**, depends on the nature of *R'* and on the reaction medium. The acyloxadiazoles **54** (*R* = Me, Ph) and *N*-methyl-*N*-phenylhydrazine react in acetic acid leading directly to triazoles **57** (*R* = Me, Ph) as a result of a series of reactions including: formation of both hydrazone isomers **55**; acid-catalyzed isomerization in the hydrazone moiety; the rearrangement of **55Z** into **56**; and demethylation of this latter into the final product [82JCS(P1)165; 90UP1]. In the reaction between the oxadiazole **54** (*R* = Ph) and *N*-methyl-*N*-phenylhydrazine in ethanol containing *p*-nitrobenzoic acid as catalyst, only the *E* hydrazone **55E** (*R* = Ph, *R'* = Me) is isolated, whereas the *Z* isomer goes directly to triazole **57**. The *E* isomer, in turn, when treated with acetic acid, gives directly the triazole compound [82JCS(P1)165]. In the absence of a demethylating agent, a rearrangement with fragmentation of the triazolium salt **56** takes place with elimination of RCN: in this case, depending on the reaction medium, a common carbodiimide intermediate produces the indazole **58** (*R'* = Me), or the semicarbazide **59** (*R'* = Me). In the reaction between the oxadiazole **54** (*R* = Ph) and *N,N*-diphenylhydrazine, both *E* and *Z* *N,N*-diphenylhydrazones are isolated. From the *Z* isomer, since the formation of the triazole is prevented, the rearrangement follows the pathway toward the formation of the corresponding indazole and/or semicarbazide (Scheme 11). The observed reactivity of an XYZ-*R* sequence seems a peculiarity of the hydrazone side-chain. In fact, the *Z* O-methyl-oxime **10Z** does not give any rearrangement (85JHC97).

From the 3-acetyloxadiazole **54** (*R* = Me), both *E* and *Z* phenylhydrazones **55** (*R* = Me; *R'* = H) are obtained, the *E* isomer being the predominant component. As expected, both isomers rearrange on melting into the triazole **57** (*R* = Me), whereas the base-induced rearrangement takes place preferably from the *Z* isomer only (90UP1).

b. *Isoxazole*. 3-Acylisoxazoles **60** give *E* and *Z* phenylhydrazones **61**, and their rearrangement into triazoles **62**, already reported to take place by melting with or without copper powder from **61aZ** (71BCJ185) or **61bE** (40G770) has been reinvestigated (83JHC931). By reacting with sodium ethoxide in refluxing ethanol, both hydrazone isomers **61a** (the *E* more slowly) rearrange into **62a**. By contrast, in the case of phenylhydrazones **61b**, only the *Z* isomer undergoes the base-induced rearrangement. However, both isomers **61b** rearrange on melting in the presence of copper powder. The rearrangement of some *Z* arylhydrazones of 3-benzoyl-5-

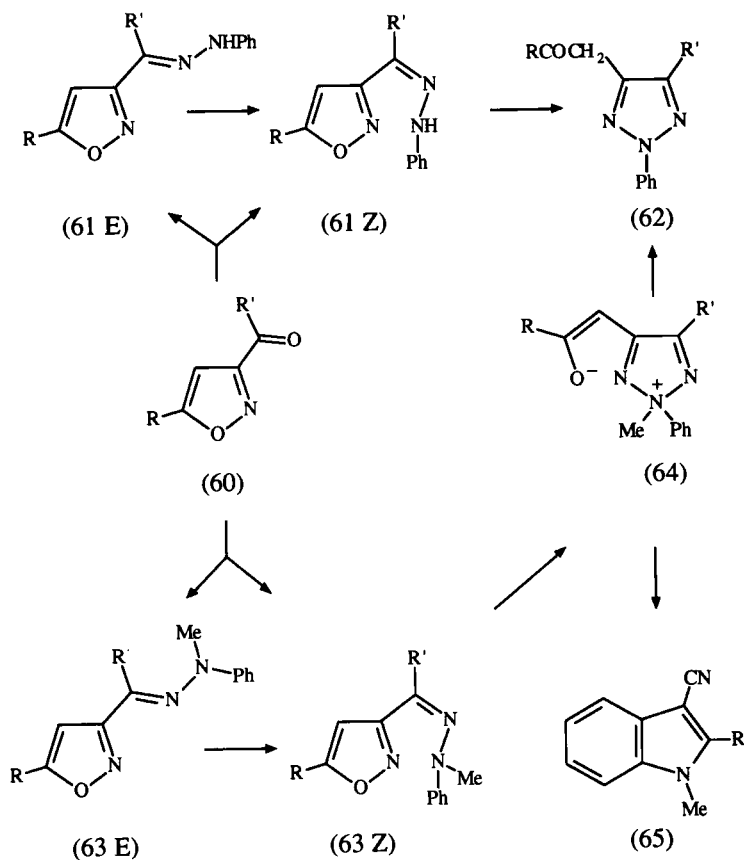


SCHEME 11

phenylisoxazole has been also studied mechanistically [87JCS(P2)537; 88JCS(P2)1683] (Section II,B,3).

Regarding the *N*-methyl-*N*-phenylhydrazone side-chain, a marked reactivity is pointed out in the reaction that rearranges **63Z** (isolated only when $\text{R} = \text{R}' = \text{Ph}$) into the triazolium salt **64** (83JHC931). The direct isomerization-rearrangement of **63E** into **62** takes place on refluxing in acetic acid, that is, in a medium where the demethylation is possible. In the absence of a demethylating agent, the isomerization-rearrangement results in 3-cyanoindoles **65**, the formation of which probably arises from a fragmentative reorganization of the triazolium salt **64** and/or of an azirine-type intermediate, the $\text{R}'\text{CN}$ species being eliminated (Scheme 12) (83JHC931).

On reacting with aqueous bases or acids, isoxazolin-5-one phenylhydra-

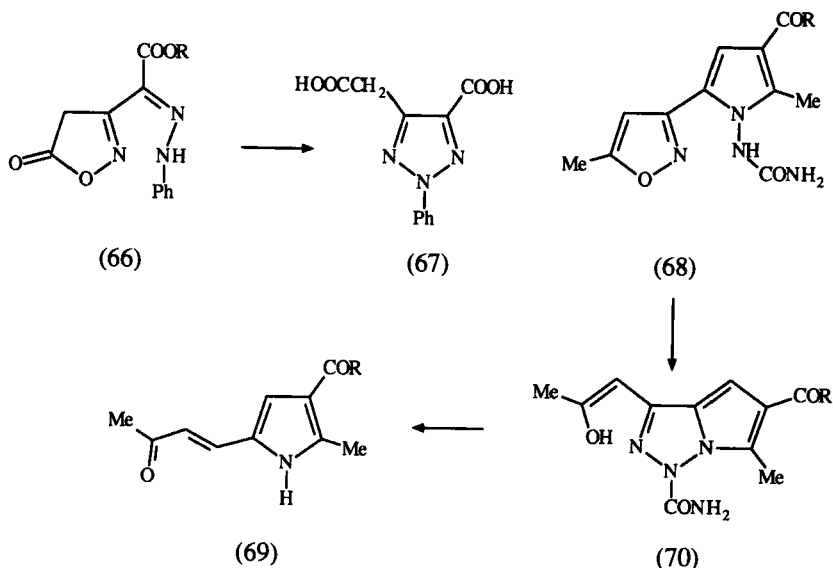


a : R = R' = Ph ; b : R = R' = Me

SCHEME 12

zones **66** rearrange into dicarboxytriazole **67** (Scheme 13) (73IZV2060); in this reaction, the presence of open-chain hydrolytic intermediates seems unlikely. On refluxing in DMF in the presence of potassium *t*-butoxide, *N*-ureido-3-pyrrolylisoxazoles **68** (R = Me, OEt) rearrange into the pyrroles **69**. A base-induced rearrangement involving the CNN sequence is suggested, where expected rearranged triazoles **70** should undergo subsequent fragmentation (Scheme 13) (91H1973).

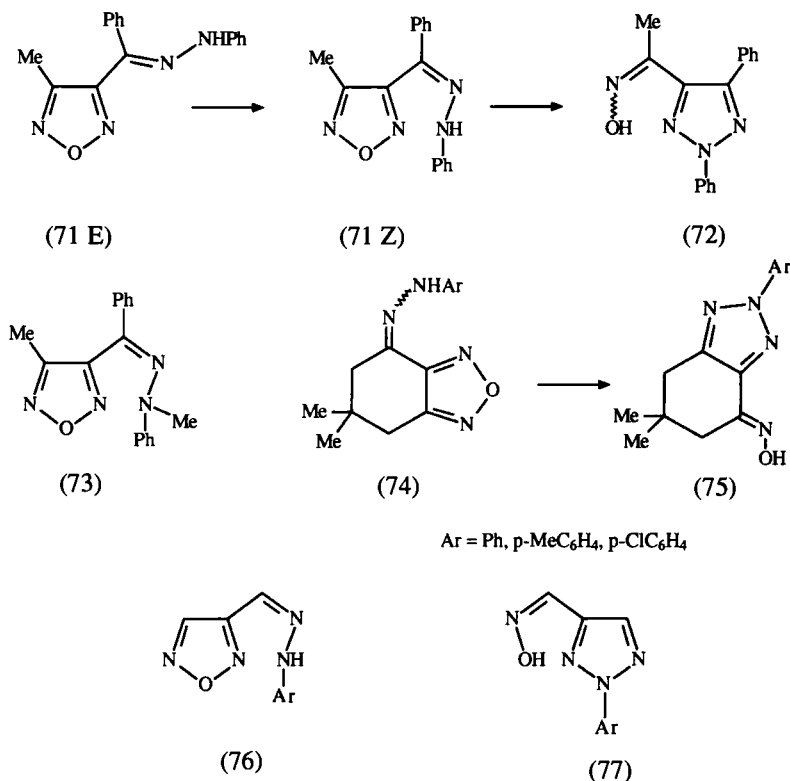
c. *1,2,5-Oxadiazole*. Unlike phenylhydrazones of 3-acetyl-4-methylfuran, which rearrange only under forced conditions (sodium salt, DMSO at 140°C) [67JCS(C)2005], phenylhydrazones **71E** and **71Z** re-



SCHEME 13

arrange into a mixture of the oxime isomers **72** by a reaction with sodium ethoxide in refluxing ethanol (Scheme 14) (90UPI). On the other hand, the *Z* *N*-methyl-*N*-phenylhydrazone **73** does not show reactivities similar to those observed in the 1,2,4-oxadiazole or isoxazole series (90UPI). In the alicyclic series, *E* and *Z* arylhydrazones **74** are reconsidered (Scheme 14) (85HCA1748). On reacting with sodium ethoxide in refluxing ethanol, the rearrangement of **74** into *E* oximes **75** is effected in very good yields from both hydrazone isomers, without substantial differences in reaction rates. An attempt to carry out a photoinduced rearrangement of the *Z* isomer (**74Z**; Ar = Ph) is also reported, presuming the occurrence of a pericyclic reaction as a [1,3]-H sigmatropic shift. However, besides photodegradation products, the irradiation causes only the configurational isomerization at the hydrazone moiety (85HCA1748).

These results show the greater stability of a 1,2,3-triazole compared with a 1,2,5-oxadiazole. As confirmation, CNDO/2 calculations on model compounds **76** and **77** are also reported. This approach shows that (a) the triazole **77** is about 20 kcal mol⁻¹ more stable than the oxadiazole **76** and (b) the π bond order of the O—N bond is lower than that of N—N (85HCA1748). The occurrence of a rearrangement by electronic impact is also shown: in the mass spectra of **74Z** the fragment at m/z (M-17)⁺ is ascribed to the formation of the rearranged product (85HCA1748).

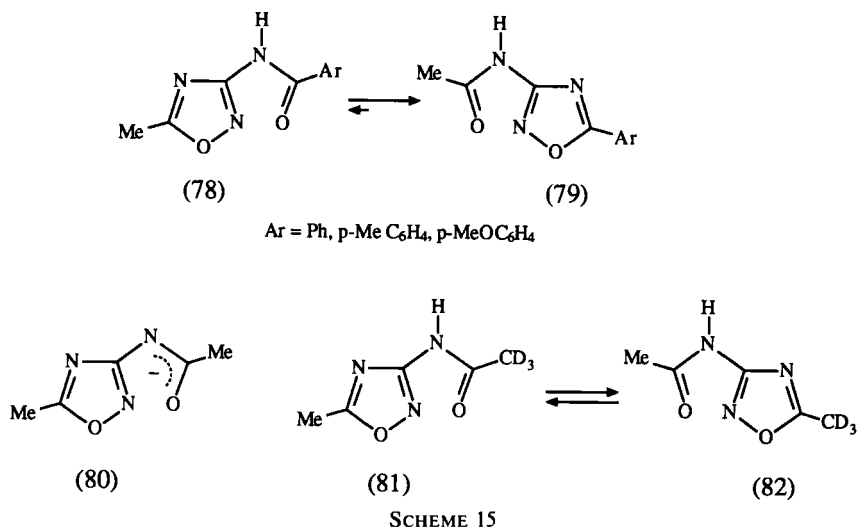


SCHEME 14

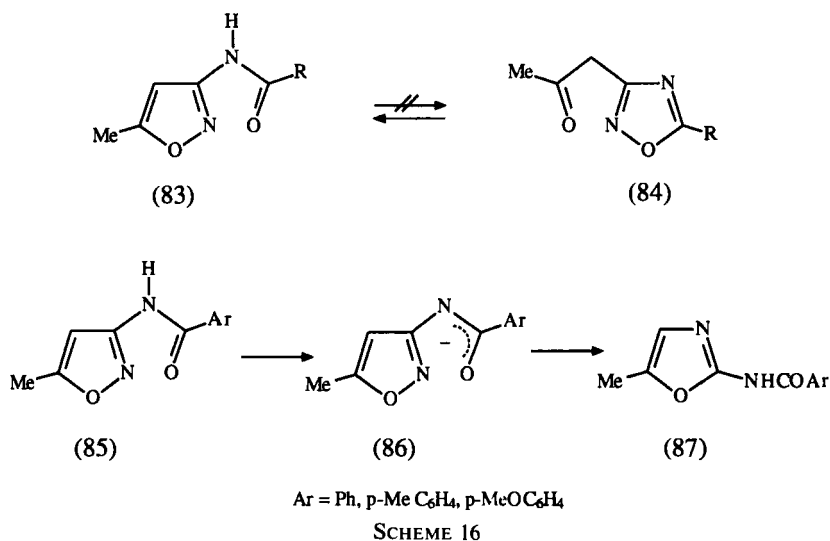
3. Rearrangements Involving a Side-Chain NCO

a. *1,2,4-Oxadiazole*. The expected isoheterocyclic (ring-degenerate) equilibrium (75JHC985) now has been extended to some 3-arylaminooxadiazoles (**78**) and to their counterparts 3-acetylmino derivatives (**79**), observing that the 5-aryl substituted oxadiazole is the predominant component (89H737). The photochemical reactivity of these compounds will be discussed separately (II,A,10). The fully degenerate rearrangement in anion **80** (75JHC1327) has been theoretically investigated (91H1547). Moreover, the rearrangement of the trideuterioacetylaminooxadiazole **81** into an equilibrium mixture of equimolar amounts of **81** and **82** is also shown (Scheme 15) (Section II,B,5).

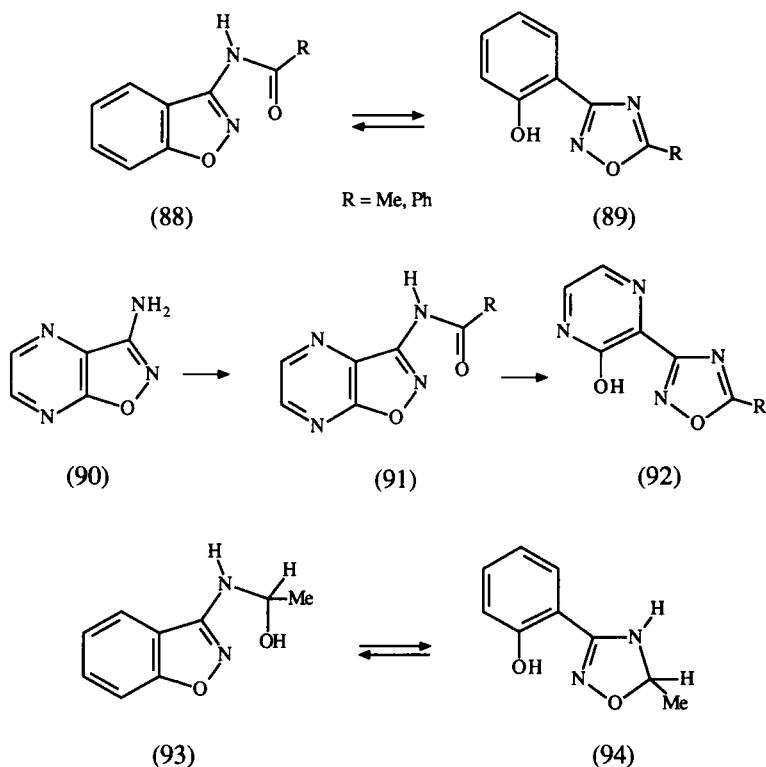
b. *Isoxazole*. Rearrangements of 3-acylaminoisoxazoles into 1,2,4-oxadiazoles according to Eq. **83** \rightarrow **84** are not known. By contrast, the



reverse rearrangement (that is, from oxadiazoles having a CCO side-chain) does work (Section II,A,4). This result agrees with the greater stability of isoxazole compared with 1,2,4-oxadiazole. On reacting with potassium *t*-butoxide in DMF at 110°C, 3-arylaminoisoxazoles **85** rearrange into 2-arylaminoxazoles **87** (91H1765), likely by a thermally induced isoxazole-to-oxazole rearrangement of anion **86** (Scheme 16).



A different reactivity is reported for benzisoxazoles (or benzo-like condensed systems). Referring to the equilibrium $88 \rightleftharpoons 89$, which is essentially shifted toward the oxadiazole component by anionic bases (73JHC957), formation of **92** from the 3-amino compound **90** and formic acid or acetic anhydride (82M731) could arise through the 3-formylamino **91** ($R = H$) or 3-acetylamino **91** ($R = Me$) intermediates, respectively. A similar process is recognizable in the rearrangement of **93** into **94** by means of sodium hydroxide at room temperature [84JCS(F2)763], the driving force being in the stabilization of the anionic form of **94** (Scheme 17). (For the reverse reaction, see Section II,A,4.)



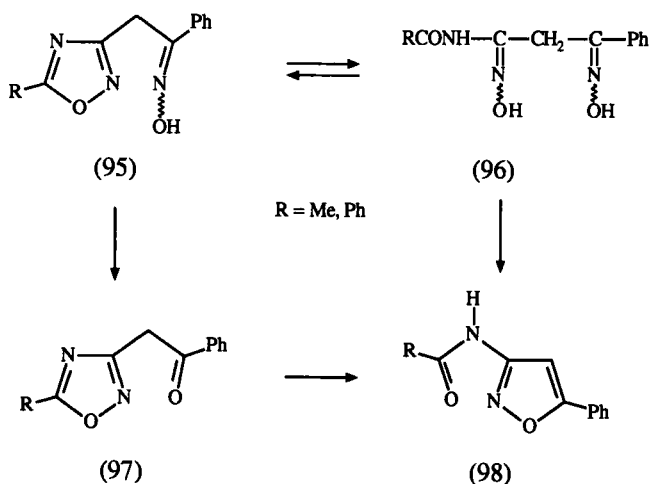
SCHEME 17

c. *1,2,5-Oxadiazole*. According to this pattern, acylaminofurazans **9** should rearrange into 3-acyl-1,2,4-oxadiazoles oximes **8** (Scheme 3). How-

ever, as expected on the basis of the different stability of the two heterocycles, examples of this type are not known; By contrast, the reverse rearrangement is a well-known reaction (Section II,A,1), and is shown to be irreversible.

4. Rearrangements Involving a Side-Chain CCO

a. *1,2,4-Oxadiazole*. 3-Acetyloxadiazoles **84** (R = isopropyl, cyclohexyl, CH₂OMe) rearrange into acylaminoisoxazoles **83** (Scheme 16) (83M373). The reaction is realized by using potassium *t*-butoxide in tetrahydrofuran or sodium methoxide in methanol at room temperature and is considered as proceeding from the enolate anion. As mentioned above, the reverse reaction does not take place, except in the benzisoxazole series. A rearrangement involving a CCO side-chain could be recognized in the reaction of oximes of 3-phenacyloxadiazoles (**95**) with hydrochloric acid, by which 3-acylaminoisoxazoles (**98**) are directly obtained (Scheme 18) (81T1415). Although not excluding the suggested open-chain species **96**, the reaction could involve the intermediacy of 3-phenacyloxadiazoles (**97**), which in turn would undergo an acid-induced rearrangement into **98** via the enolic side-chain reacting on the protonated oxadiazole.

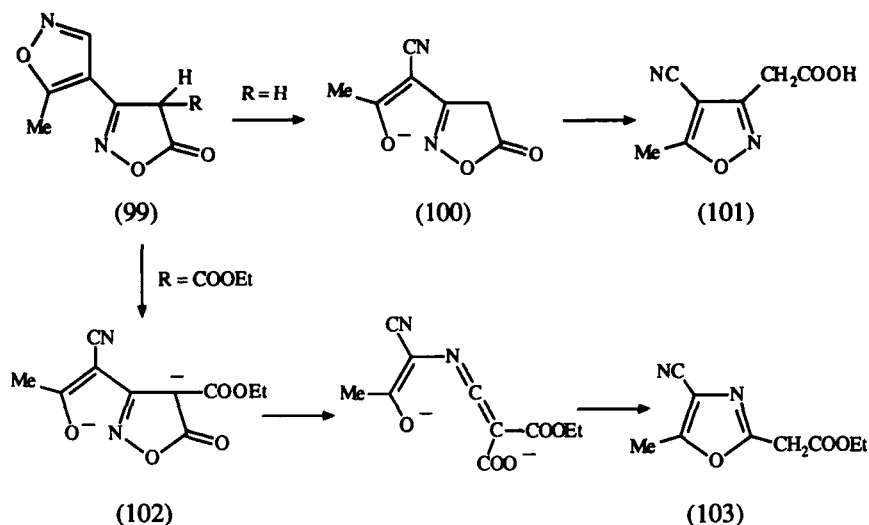


SCHEME 18

The equilibrium **93** \rightleftharpoons **94** pertains on one hand to an oxadiazoline containing a CCO side group (**94**), and on the other to a benzisoxazole that has a saturated NCO chain (**93**) (Scheme 17). The reaction resembles the

more general one pointed out for 3-acylaminobenzisoxazoles (**88**) for which the equilibrium position depends on the substituent R (methyl or phenyl) and on the base used (anionic or not) (73JHC957). In our case, the rearrangement of **93** into **94** occurs in aqueous sodium hydroxide in ethanol at room temperature. On the other hand, benzisoxazole **93** was reached "by accident" in an attempt to synthesize the oxadiazoline **94** by the reaction of the *o*-hydroxybenzamidoxime with acetaldehyde [84JCS(F2)763].

b. *Isoxazole*. In the isoxazole series, the CCO side-chain should produce an isoheterocyclic (ring-degenerate) rearrangement. However, such a reaction does not appear widespread. An example regarding an isoxazolin-5-one is shown in Scheme 19; here, different structural patterns



SCHEME 19

direct the rearrangement toward distinct pathways [88JCS(P1)1875]. On reacting with aqueous sodium hydroxide, compound **99** (R = H) yields the isoxazole **101** by a typical rearrangement of anion **100**, which in turn arises from the base-promoted ring opening of the 3-unsubstituted isoxazole. By contrast, compound **99** (R = COOEt) does not give this rearrangement, since the reaction with potassium *t*-butoxide in DMF produces the oxazole **103**, as a result of a Beckmann-type rearrangement of the stabilized dianion **102** followed by ring closure.

c. *1,2,5-Oxadiazole*. As anticipated (81AHC141), literature (51G499) about the *supposed acid-induced* rearrangement of furazan ketones **26** ($R^1 = R^3 = \text{Ph}$; $R^2 = \text{H, Ph}$) into the corresponding isoxazoles **24** through open-chain intermediates **27** has been critically reviewed [83JCS(P1)483]. The supposed furazan ketones that were reported to take place in the oximation of 3-acylisoxazoles **24** ($R^1 = R^3 = \text{Ph}$; $R^2 = \text{H, Ph}$) proved to be isoxazole oximes **25** (Scheme 5) (Section II,A,1). Therefore, the results in the literature must be considered to be a simple hydrolysis of the oxime group. On the other hand, true furazan ketones **26** do not give the formerly claimed rearrangement [83JCS(P1)483].

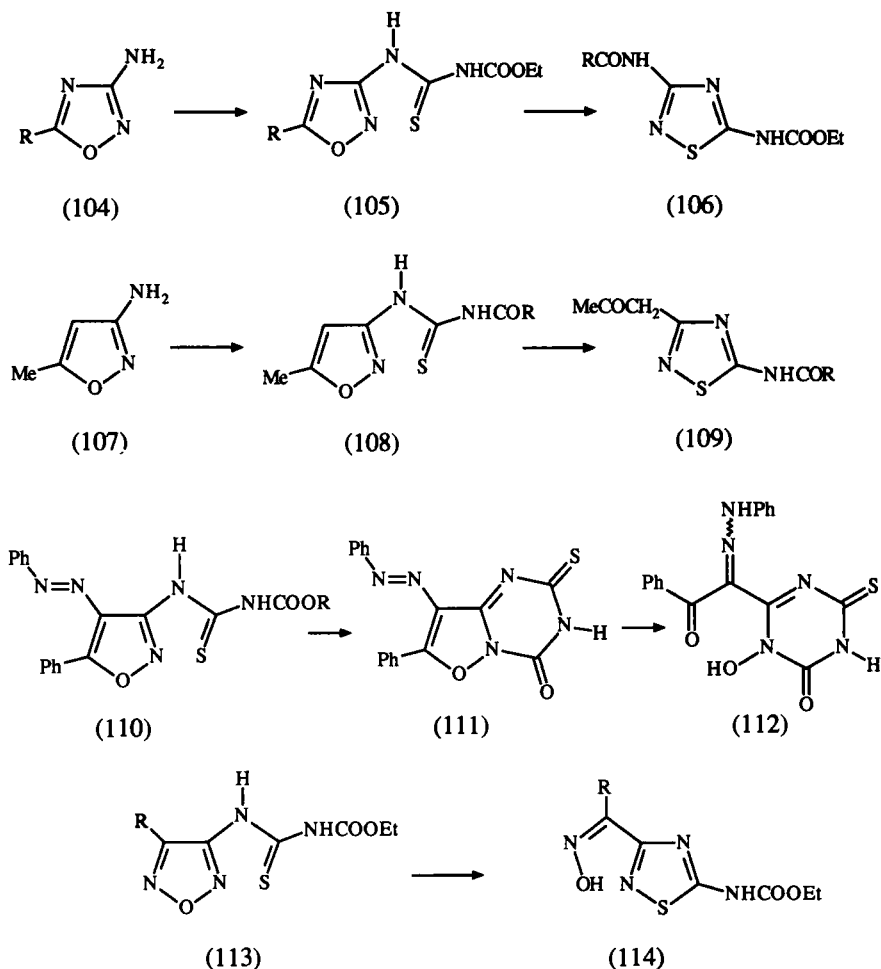
5. Rearrangements Involving a Side-Chain NCS

a. *1,2,4-Oxadiazole*. Due to the strong sensitivity of the 1,2,4-oxadiazole toward rearrangements, and to the high nucleophilicity of sulfur, 1,2,4-oxadiazoles bearing an NCS side-chain are not reported as such. As anticipated (81AHC141), the reaction between 3-aminooxadiazoles **104** ($R = \text{Me, Ph}$) and ethoxycarbonyl isothiocyanate yields directly thiadiazoles **106**, whereas thioureas **105** are not isolated (Scheme 20) (86H3433). On the basis of these findings, the thiadiazole structure (**106**; $R = \text{Ph}$) is therefore assigned (86H3433) to the reaction product formerly described as a thiourea (**105**; $R = \text{Ph}$) (74ZC94).

b. *Isoxazole*. The reaction between the aminoisoxazole **107** and ethoxycarbonyl isothiocyanate gives the thiourea **108** ($R = \text{OEt}$), which easily rearranges into the thiadiazole (**109**) (Scheme 20) (86H3433). Similarly, aroyl isothiocyanates produce aroylthioureas **108** ($R = \text{Ar}$). From these, by a reaction with POCl_3 at reflux, both *E* and *Z* (3-(2-chloropropenyl)-5-aroylethiadiadiazoles directly result via a previous rearrangement of thioureas into thiadiazoles. On the other hand, the aroylthiourea **108** ($R = \text{Ph}$) rearrange into the corresponding thiadiazole (**109**) on simple reflux in toluene (88MI1).

With this background, we suggest some caution in interpreting the reactions between 3-amino-5-phenyl-4-phenylazoisoxazole and isothiocyanates in refluxing acetone, which would lead to thioureas **110**, the reactivity of which does not involve the NCS side-chain [77ZN(B)311]. Surprisingly, it is reported that compounds **110** ($R = \text{Me, Et}$) do not cyclize on heating or on reacting with bases. On refluxing in acetic acid, formation of **112** from the ring opening of **111** is claimed, however (Scheme 20) [77ZN(B)311].

c. *1,2,5-Oxadiazole*. The reactivity of thioureas **113** ($R = \text{Me, Ph}$) has been also considered (86H3433). Analogous to what is observed for

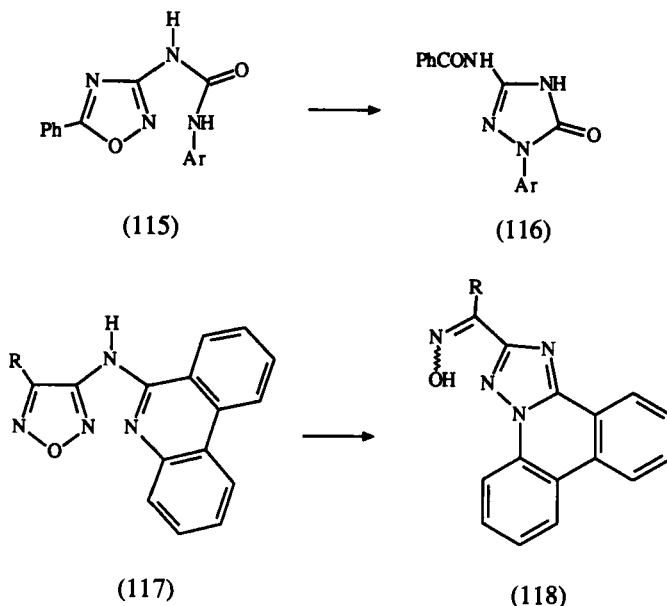


SCHEME 20

phenylthiureas [77JCS(P1)1616], the rearrangement of **113** with aqueous bases at room temperature leads to *Z* oximes **114**, where the configuration of the CNO moiety of the starting ring is maintained (Scheme 20) (86H3433).

6. Rearrangements Involving a Side-Chain NCN

Some *N*-1,2,4-oxadiazolyl-*N'*-arylureas (**115**) have been synthesized, and their base-induced rearrangement into the benzoylamino-1,2,4-tria-



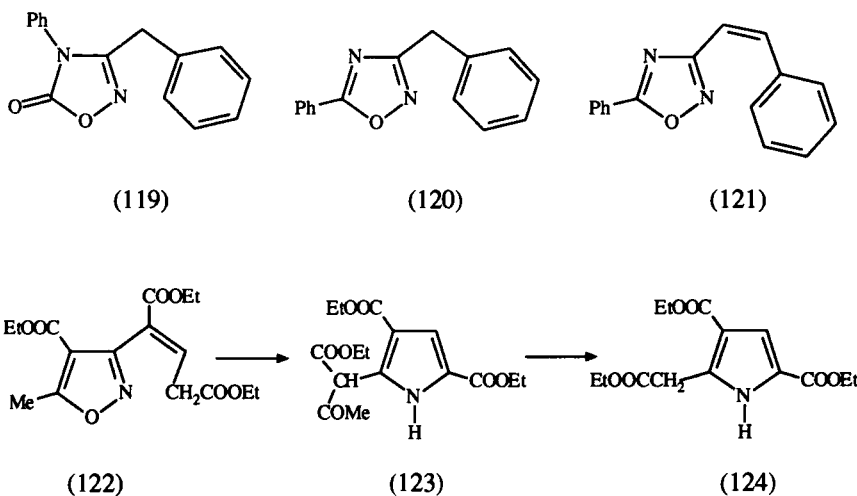
SCHEME 21

zolin-5-ones (**116**) (Scheme 21) (70CC866) has been mechanistically studied [90JCS(P2)1289] (Section II,B,4). As for the 1,2,5-oxadiazole system, phenanthridines **117** (R = Me, Ph) rearrange into oximes **118** (Scheme 21) (90H869). Here, because of the low reactivity of the ring, the reaction occurs under forced conditions (potassium *t*-butoxide in refluxing DMF) and produces the *E* oxime (R = Me), or a mixture of both the *E* and the *Z* isomers (R = Ph).

7. Rearrangements Involving a Side-Chain CCC

In the 1,2,4-oxadiazole series, rearrangements involving a three-carbon atoms side-chain are not known. In a photochemical approach, 3-benzyl-oxadiazoles **119** and **120** containing a nonconjugated side group are considered (Section II,A,10). However, the presumed photoinduced heterocyclization involving the benzyl group does not take place (70JHC59; 88JHC1551). On the other hand, the styryloxadiazole **121** containing a four-carbon atoms side-chain does give the photoinduced heterocyclization involving the styryl group (90JHC861) (Section II,A,10).

The nucleophilicity of an attacking carbon atom in a CCC-side-chain is



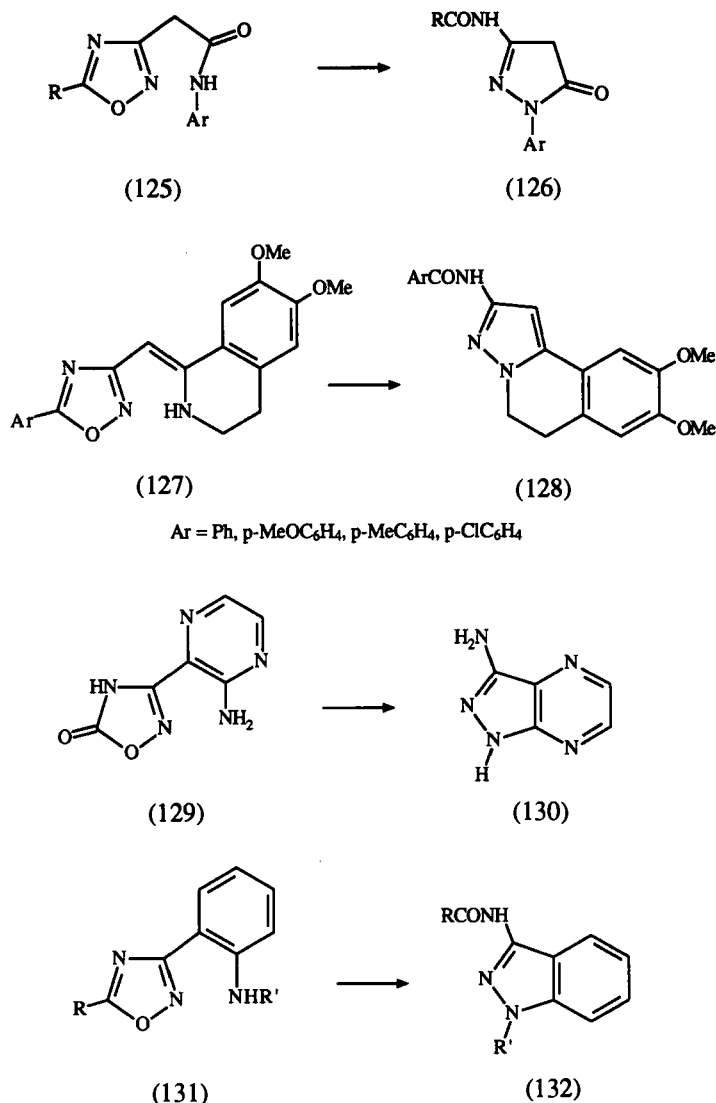
SCHEME 22

pointed out in the rearrangement of isoxazole **122** into pyrrole **123** by the reaction with DBU in ether (Scheme 22) [86JCS(P1)927]. The rearrangement finds a driving force in the stabilization of the negative charge in the rearranged enolate. By using ethanolic potassium hydroxide or sodium ethoxide, the reaction gives directly the pyrrole **124**, which is also obtained from **123** under similar conditions.

8. Rearrangements Involving a Side-Chain CCN

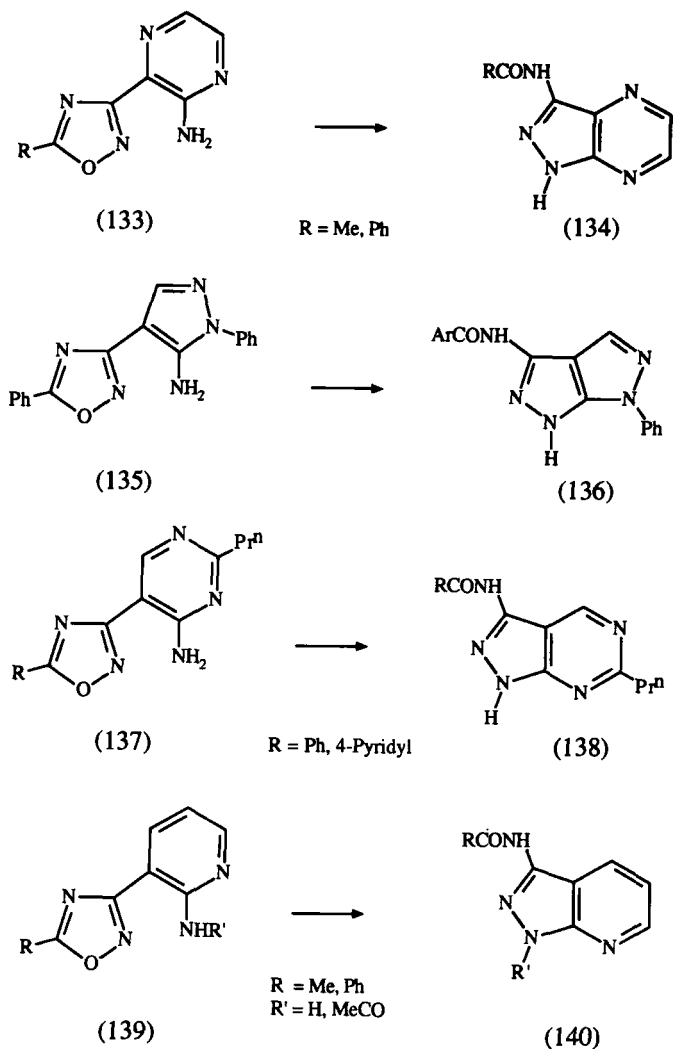
Typical rearrangements of 1,2,4-oxadiazoles involve either an unsaturated (ring-conjugated) or a saturated (ring-unconjugated) side-chain. Examples involving an unsaturated chain, many of which have the C=C group as part of an aromatic ring, are presented first (Schemes 23 and 24). Substrates bearing a saturated side-chain are discussed for comparison (Scheme 25). Some comments on mechanisms then will be reported separately (Section II,B,6).

The rearrangement of oxadiazoles **125** (R = alkyl; Ar = Ph, trichlorophenyl) into **126** takes place by a reaction with inorganic bases (83MIP8202198; 84JOC5247). In the absence of bases, or by using organic bases such as triethylamine, the reaction does not occur. Oxadiazoles **127**, which contain an annulated side-chain, rearrange into the annulated pyrazoles **128** on refluxing in xylene, and kinetic data (in *n*-butanol at 110°C) are compared with those of the rearrangement **145** → **146** involving



SCHEME 23

the corresponding saturated side-chain [86JCS(P1)9]. Compound **129** rearranges into **130** (with poor yields) on refluxing in DMF in the presence of bases (sodium ethoxide or methoxide) (82M731). Analogously, compounds **133** (82H339), **135**, **137**, and **139** rearrange (in very good yields) into the annulated pyrazoles **134**, **136**, **138**, and **140**, respectively, by reflux in DMF in the presence of sodium hydroxide [82JCS(P1)759].



SCHEME 24

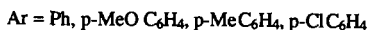
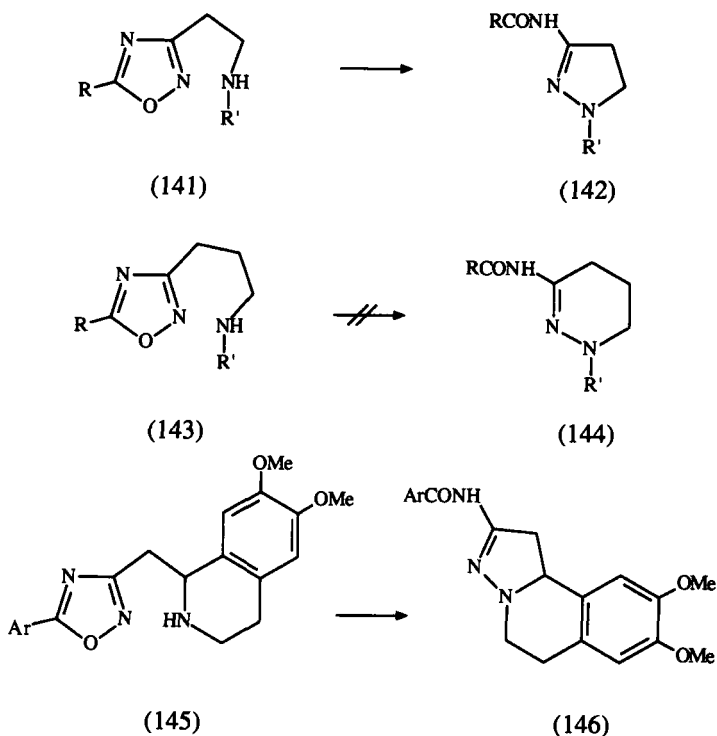
The generalized rearrangement of oxadiazoles **131** into 3-acylaminoindazoles **132** was studied taking into account several substituents R and R'. Some considerations on structural factors affecting the reaction were emphasized [82JCS(P1)759]. The *N*-alkyl derivatives rearrange on melting or on heating at 150°C in DMF and are about 10 times more reactive than the corresponding substrates having the primary amino group. As expected, because of the absence of hydrogen atoms with acid character, no base catalysis is observed; moreover, when the nucleophilicity of the

nitrogen of the amino group decreases, the reactivity also decreases. When strongly electron-withdrawing groups are linked to the nitrogen of the CCN sequence, owing to a certain acid character of the hydrogen atoms, a strong solvent effect and base catalysis are observed. In nonpolar solvents the rearrangement rate is negligible, even at 150°C. However, the reaction rate increases in DMF or DMSO solvents, or in xylene in the presence of piperidine or triethylamine; moreover, oxadiazoles **131** ($R = \text{Me, Ph}$; $R' = \text{COMe, CPh}$) rearrange very easily in the presence of hydroxide base (79JHC783; 90ACH795). In the rearrangements of 3-heteroarylaminooxadiazoles **133**, **135**, **137**, and **139**, because of the greater mobility of the hydrogen atom of the N—H, base catalysis even for the primary amino group is observed. Considering oxadiazoles **131**, rearrangement rates at 150°C in DMF increase on going from the 5-alkyl to the 5-phenyl substituted substrates. Moreover, substituents at the C(5)-aryl ring (**131**; $R = p\text{-XC}_6\text{H}_4$, $R' = \text{PhCH}_2$) show a good Hammett correlation, with a ρ value (0.89) comparable to that observed in the rearrangement of **141**, which has a saturated side group [82JCS(P1)759].

Regarding oxadiazoles bearing a saturated side-chain (Scheme 25), in the generalized rearrangement of **141** into **142** electronic effects of R and R' agree with the internal nucleophilic substitution pattern: the reaction rate is increased by an electron-donor R' , which increases the nucleophilicity of the nitrogen atom, and is lowered by electron-withdrawing groups [79JCR(M)0801, 79JCR(S)64]. As expected, electronic effects of the substituent at the C(5) of the oxadiazole show an opposite pattern. A determining role in a positive outcome for the rearrangement is the length of the side-chain; in this context, oxadiazoles **143** do not rearrange into **144** (84ACH239; 86JST215), essentially because of entropic and directional factors: nitrogen atoms that must form the new bond would interact better in a planar five-membered than in a six-membered nonplanar transition state. In support of this are X-ray diffraction data (86JST215). By comparing the reactivity of compounds **145** with that of the structurally related **127**, it is emphasized that the reaction $\text{145} \rightarrow \text{146}$ turns out to be about 20 times faster than the reaction $\text{127} \rightarrow \text{128}$, and this difference is due to the lower nucleophilicity of the attacking nitrogen in compounds **127**. Moreover, in both substrates, electron-releasing substituents at the C(5)-aryl moiety decrease reactivity, whereas electron-withdrawing substituents increase it, comparable ρ values in both systems being observed [86JCS(P1)9] (See also Section II,B,6.)

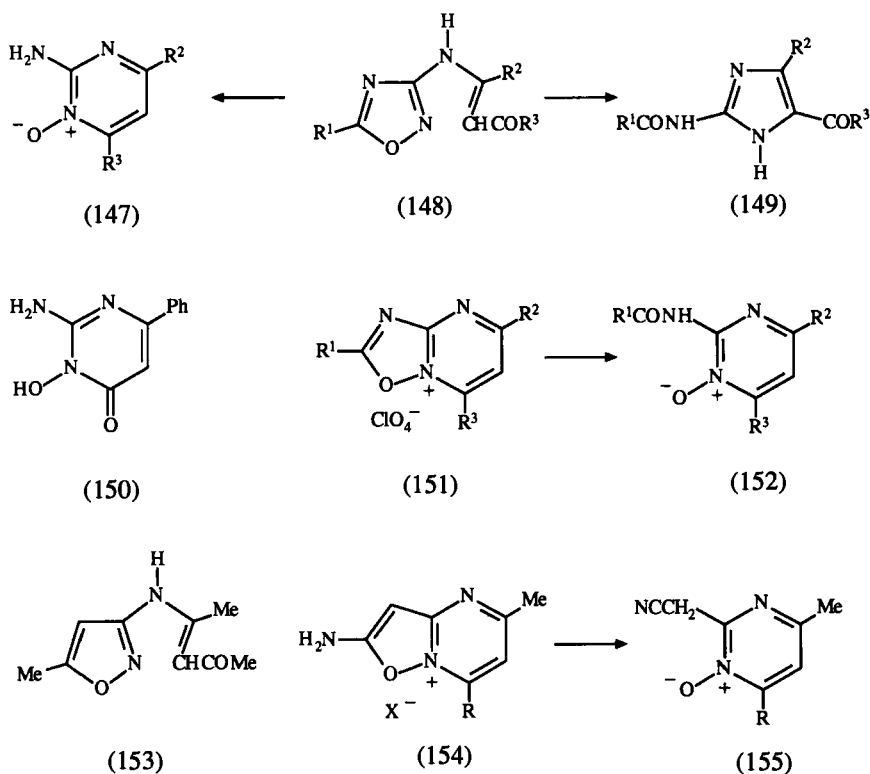
9. Miscellaneous

On reacting with potassium *t*-butoxide in DMF at 110°C enaminketones **148** rearrange into acylaminoimidazoles **149** (72TL4959; 74T3859;



SCHEME 25

78JA4209; 81AHC141). A different process occurs when some enaminoketones react with sodium ethoxide in ethanol. Compounds **148** ($R^1 = R^2 = \text{Me}$; $R^3 = \text{Me, Ph}$) give aminopyrimidine *N*-oxides **147**, whereas the enaminoester **148** ($R^1 = \text{Me}$, $R^2 = \text{Ph}$, $R^3 = \text{OEt}$), in addition to the corresponding imidazole **149**, gives the *N*-hydroxypyrimidine **150** (Scheme 26) [86JCS(P1)17]. Although a detailed mechanism was not explored, the formation of the pyrimidine ring is explained by nucleophilic attack of the enolate oxygen on the pivotal nitrogen in a cyclic seven-membered intermediate, or, perhaps better, by nucleophilic attack of the N(2) annular nitrogen on the carbonyl carbon of the side-chain [86JCS(P1)17]. The rearrangement into a pyrimidine *N*-oxide also takes place on reacting enaminoketones **148** with perchloric acid [86JHC1175]. In some cases ($R^1 = \text{Ph}$) oxadiazolium salts **151** are isolated, and subsequent neutralization in an aqueous medium produces acylaminopyrimidines **152**. In other instances ($R^1 = \text{Me}$), the reaction leads directly to aminopyrimidine *N*-oxides **147**. At least formally, in such a rearrangement

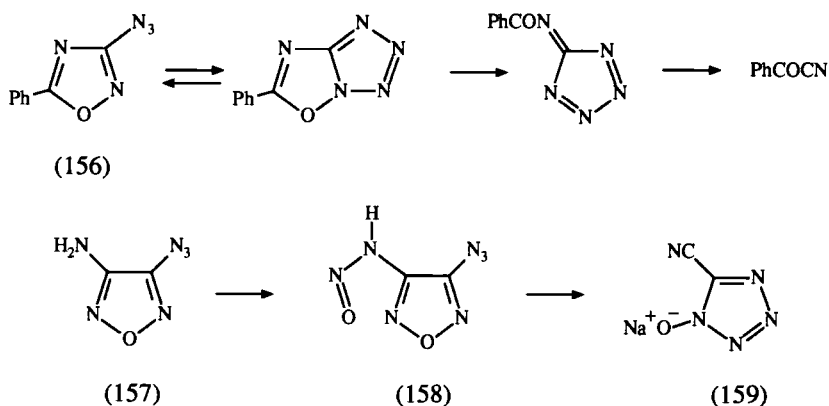


SCHEME 26

the enaminoketone side group acts as electrophilic substrate, whereas the oxadiazole acts as the nucleophilic component. Moreover, although not documented, the oxadiazole would likely suffer ring-opening at the O—C(5) bond.

Regarding the isoxazole series, rearrangements of the enaminoketone **153** into an imidazole or a pyrimidine *N*-oxide does not take place [81AHC141; 86JCS(P1)17]. On the other hand, isoxazolium salts rearrange when special substituents are present; thus, neutralization of **154** leads to the pyrimidine *N*-oxides **155** through a fragmentation of the isoxazole moiety (Scheme 26) (83JOC575). In the 1,2,5-oxadiazole series, rearrangements involving enaminoketones or their corresponding oxadiazolium salts are not known (80UKZ637; 84H1571).

Pyrolysis of the 3-azidooxadiazole **156** results in the formation of molecular nitrogen and benzonitrile. The reaction assumes an initial azidotetrazole equilibrium, followed by O—N bond breaking and subsequent fragmentation and isomerization (Scheme 27) (82TL121). On reacting with



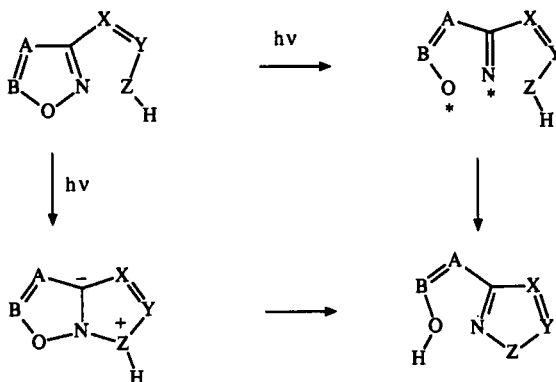
SCHEME 27

an excess of sodium nitrite in acetic acid, the azidoaminofurazan **157** rearranges into the sodium salt of the hydroxycyanotetrazole **159** (Scheme 27). Here, the reaction is represented as proceeding via an azidonitrosoamine intermediate (**158**), from which deamination with consequent O—N bond cleavage into a furazane-tetrazole species would take place (88CHE1378).

10. A Photochemical Approach

Photorearrangements of five-membered heterocycles leading to ring photoisomerizations are extensively reported and proceed by some characteristic and generalized mechanisms (80MI1). According to the general pattern of our treatment, in this section we will consider the photochemical approach to rearrangements of O—N-bond-containing heterocycles with the participation of a three- or four-atoms side-chain. As expected, in addition to a concerted mechanism, the photorearrangement can follow two distinct pathways (Scheme 28). According to one, the photoreaction proceeds by photolysis of the O—N bond of the rearranging ring; the intermediate species (zwitterion or diradical) then collapses into the rearranged product through a heterocyclization with the XYZ side group. According to the other, the photoreaction proceeds by a photoinduced heterocyclization into a bicyclic intermediate, followed by the subsequent breaking (thermal or photochemical) of the O—N bond. Significant examples of photorearrangements of the type under consideration are reported for 1,2,4-oxadiazoles.

The photochemical reactivity of 1,2,4-oxadiazoles (**161**) in methanol at 254 nm mainly consists of two different photoreactions, which depend on

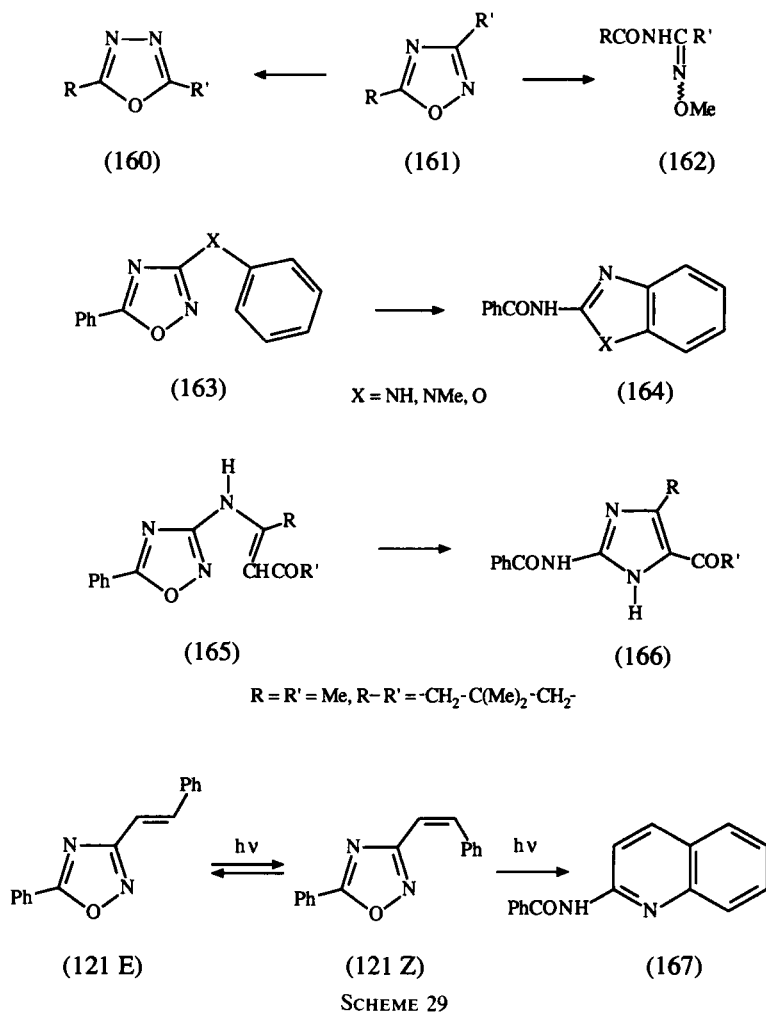


SCHEME 28

the nature and position of substituents. The ring photoisomerization into 1,3,4-oxadiazole (**160**) occurs only when the 1,2,4-oxadiazole contains tautomerizable groups in the position 3; in different cases, formation of open-chain products (**162**) by the reaction of the solvent with the photolytic intermediate will be the predominant photoreaction (Scheme 29) (68TL2421; 88JCS(P1)1313, 88JHC931).

3-*N*-Phenylaminooxadiazoles **163** ($X = \text{NH}$, NMe), in addition to **160** ($R = \text{Ph}$, $R' = \text{NHPh}$) and **162** ($R = \text{Ph}$, $R' = \text{NMePh}$), respectively, produce rearranged benzimidazoles **164** ($X = \text{NH}$, NMe) (88JHC931). In this context, it is worth pointing out that the 3-phenylaminooxadiazole **163** ($X = \text{NH}$) does not give the thermal or base-induced rearrangement involving the NCC side-chain (74MI1), clearly because of the low nucleophilicity of the attacking carbon atom. Photorearrangements into imidazoles (**166**) also take place in the irradiation of enaminoketones **165** (Scheme 29) (88JHC1551). For such substrates, the base-induced rearrangement into imidazoles represents a well-supported reaction (Section II,A,9). Irradiation of the 3-*O*-phenyloxadiazole **163** ($X = \text{O}$) produces the rearranged benzoxazole **164** ($X = \text{O}$), together with the solvolysis product. By contrast, irradiation of 3-benzoyloxadiazole **120** mainly gives the solvolysis product, whereas the presumed photorearrangement involving the benzyl moiety does not take place (88JHC1551). Moreover, in the irradiation of **119**, the nitrene species arising from O—N bond photolysis and extrusion of carbon dioxide does not give heterocyclization with the benzyl moiety. Here, the heterocyclization engages the phenyl ring bound at N(4) to produce the 2-benzylbenzimidazole (70JHC59).

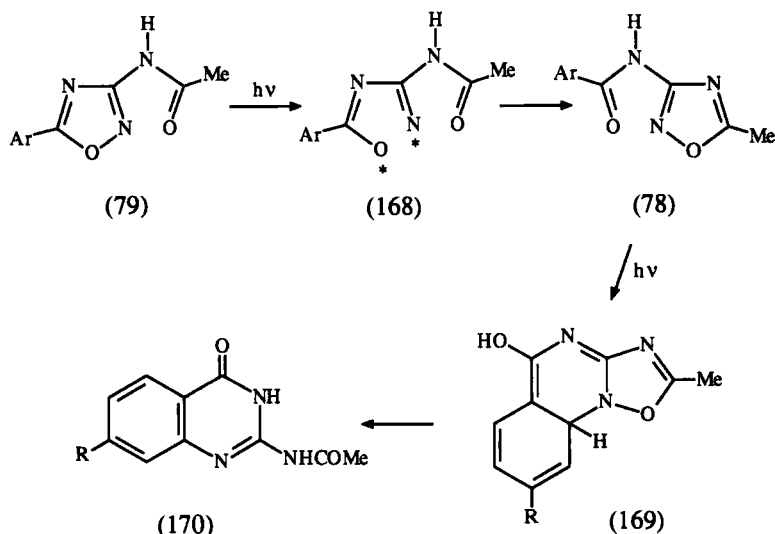
All these results are explained by assuming an initial photolysis of the ring O—N bond to produce an intermediate species (zwitterion or nitrene),



from which photoproducts will derive; clearly, the formation of rearrangement products occurs only when the heterocyclization involving the side group is assisted by an aromatic transition state (70JHC59; 88JHC1551). By a similar mechanism the 3-styryloxadiazole (**121E**) photorearranges into **167** (Scheme 29) (90JHC861), the heterocyclization affecting the benzene ring of the *Z* styryl group in a six-membered transition state; here, a fast photoinduced configurational isomerization is associated with the slow rearrangement process. On the other hand, irradiation of 3-styryl-5-methyl-1,2,4-oxadiazole essentially causes isomerization at the

styryl moiety and this different reactivity is ascribed to different chromophores that are activated in the 5-phenyl- or 5-methyl-substituted oxadiazole, respectively (90JHC861).

The photochemical behavior at 254 nm in methanol of 3-acylamino-oxadiazoles was also studied [89H737, 89H1301; 91JCS(P2)187]. The 3-acetyl-amino-5-aryl-(**79**) and the isoheterocyclic counterparts 3-aroylamino-5-methyl-oxadiazoles (**78**) are considered. (For the thermally induced equilibrium, see Section II,A,3.) Irradiation of aroylaminooxadiazoles **78** does not give corresponding isoheterocycles **79**, but quinazolinones **170**, directly. On the other hand, irradiation of acetylaminooxadiazoles **79** gives quinazolinones **170**, too; however, here the reaction involves the intermediacy of aroylamino compounds **78** (Scheme 30). In order to



SCHEME 30

rationalize these results, the illustrated photochemical scheme is proposed. According to this, the photochemical reactivity of 3-acetylaminooxadiazoles (**79**) affects the 5-aryl-substituted heterocycle, producing the photolytic intermediate **168**; this latter, by involvement of the NCO group of the acetyl amino moiety collapses into aroylaminooxadiazoles (**78**). By contrast, the photochemical reactivity of aroylaminooxadiazoles (**78**) affects the side aroylamino group. In this manner, a six-membered heterocyclization involving the phenyl ring leads to a tricyclic intermediate (**169**), from which the rearranged **170** forms. This different photochemical reactivity is related to different chromophores, which are activated in **79** (the

5-aryl-substituted heterocycle) and in **78** (the aroylamino group), respectively, and to different multiplicity of excited states. In this context, analysis of emission spectra and the use of quenchers and sensitizers suggests that the photorearrangement of aroylaminooxadiazoles **78** into **170** involves triplet excited states, whereas the photorearrangement of acetylaminooxadiazoles **79** proceeds via singlet excited states [91JCS(P2)187].

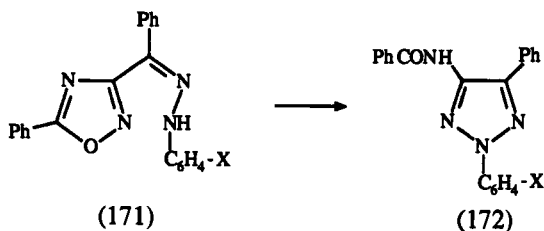
B. MECHANISTIC ASPECTS

Up to the time of the previous review (81AHC141), few results on the mechanistic aspects of rearrangements of the O—N-bond-containing heterocycles were available. Recently, a significant contribution to this topic has been made by the Spinelli group. In this section we will present a comprehensive review of the subject.

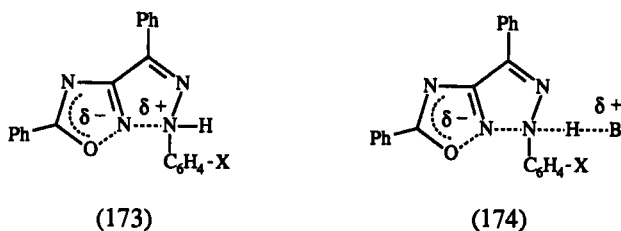
1. *Rearrangements of Z Arylhydrazones of 3-Benzoyl-5-Substituted 1,2,4-Oxadiazoles*

a. *Rearrangements of Z Arylhydrazones of 3-Benzoyl-5-phenyl-1,2,4-oxadiazole in Dioxan–Water.* The rearrangement of *Z* arylhydrazones **171** into triazoles **172** in dioxan–water in the presence of buffers at different pS^+ [an operational pH scale (69MI1)] follows two different reaction pathways. The first, uncatalyzed, occurs at low pS^+ ; the second, base-catalyzed, predominates at high pS^+ . Two consequent mechanisms have been proposed, in which the rate-determining step is represented by the formation of transition states **173** or **174** (B = base), respectively [76JHC357; 81JCS(P2)1325]. For the unsubstituted hydrazone **171Z** (X = H), a kinetic study performed in the presence of different buffers at different concentrations and at various pS^+ values indicates [81JCS(P2)1325] a reaction mechanism occurring with general-base catalysis and an apparent first-order kinetic constant (k_A), according to the equation $k_A = k_u + k_{OH}[OH^-] + k_B[B]$; (u = uncatalyzed; B = base such as borate or phenolate). The catalytic constants give an excellent Brønsted correlation with a β value of 0.46 (70MI1). In line with this, kinetic isotopic effects for rearrangements of N—H or N—D hydrazones at different pS^+ values show a ratio of $(k_A)_H/(k_A)_D$ equal to 1.8 in the pS^+ -independent range and 2.9 in the base-catalyzed one (62MI1).

The electronic effects of substituents in the phenyl ring of the arylhydrazone moiety have been studied in the range of pS^+ 3.80–11.50. The kinetic data indicate a variation of the substituent effect by varying pS^+ and show that the pS^+ ranges in which uncatalyzed and base-catalyzed paths occur



X = *p*-MeO, *p*-Me, *p*-Et, *m*-Me, *m*-Et, H, *p*-Cl, *p*-Br, *m*-Cl, *m*-Br, *m*-NO₂, *p*-CN, *p*-NO₂



are a function of the substituent [78JCS(P2)19; 79JHC359; 81JCR(M)3550, 81JCR(S)308]; consequently, Hammett correlations give different results on varying the pS^+ . At pS^+ 3.80, a good multiparameter correlation (Ingold–Yukawa–Tsuno) (69MI2; 72BCJ1198; 73JA102, 73JA5350, 73JA5357) is obtained (ρ -1.31). The low ρ value is rationalized by a balance among opposite electronic effects (on the nucleophilicity of the attacking nitrogen and on the acidity of the N—H group) exercised by substituents in the rate-determining step, according to an S_Ni type of transition state. At $pS^+ > 8.50$, two linear free-energy relationships are defined, the lowest reactivity being observed for the unsubstituted hydrazone (171; X = H). Therefore, in the range of pS^+ 8.50–11.50, Hammett plots show positive ρ values for electron-withdrawing substituents, and very low negative ρ constants for the electron-releasing ones. In a typical multiparameter correlation (Yukawa–Tsuno) at pS^+ 10.0, ρ values were $+2.19$ and -0.28 , respectively (Fig. 1) [81JCR(M)3550, 81JCR(S)308]. All these results are explained by assuming structural changes in the transition state by varying the substituent: that is, in 174, the timing of N—N bond formation and N—H bond breaking is a function of the substituent in the arylhydrazone group; on the other hand, the electronic effect of the substituent influences (with different weights) either the nucleophilicity of the attacking nitrogen atom or the acidity of the N—H group that undergoes base catalysis. Electron-withdrawing substituents cause a large increase in reactivity by increasing the acidity of the N—H; in turn, electron-

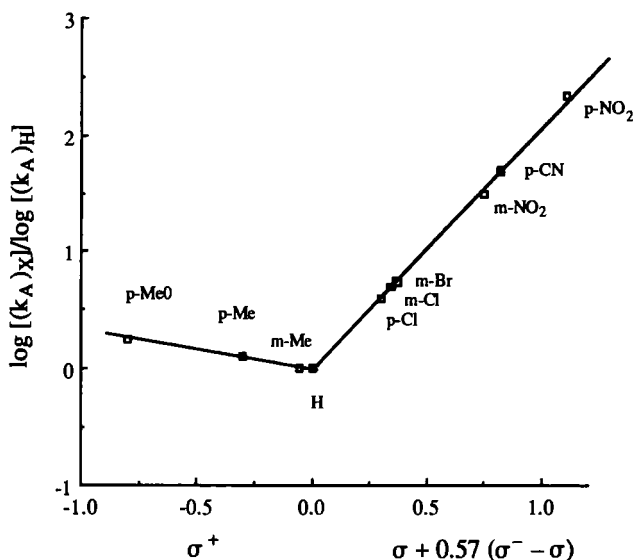
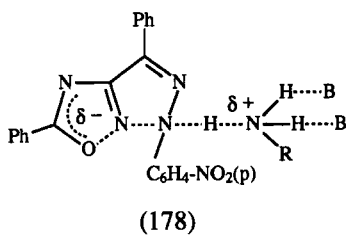
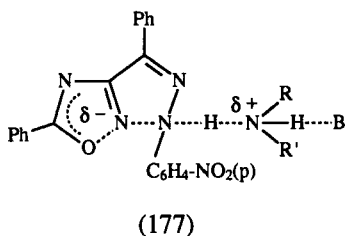
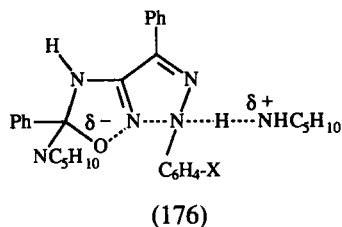
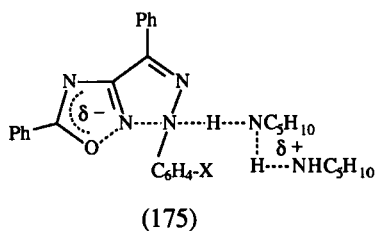


FIG. 1. Plot of Yukawa-Tsuno for the rearrangement **171** \rightarrow **172** at 313.15 K and at $pS^+ 10.0$ [81JCR(M)3550, 81JCR(S)308].

releasing substituents, even on reducing the acidity of the N—H group, will cause a small increase in reactivity by increasing the nucleophilicity of the attacking nitrogen [81JCR(M)3550, 81JCR(S)308].

b. *Rearrangements of Z Arylhydrazones of 3-Benzoyl-5-phenyl-1,2,4-oxadiazole in Benzene (or Other Solvents) in the Presence of Amines.* A kinetic study of the piperidine-catalyzed rearrangement of the unsubstituted phenylhydrazone (**171**; $X = H$) in benzene solvent indicates two reaction pathways catalyzed by one or two molecules of piperidine, respectively (80JHC801). The bimolecular reaction agrees with transition state **174** ($B = NHC_5H_{10}$); in the case of the third-order pathway, two possible actions for the second molecule of piperidine are recognized (80JHC801): a catalysis of catalysis model (64JA833; 75T2523) as in **175**, or an addition of a piperidine molecule to the C(5)—N(4) double bond of the oxadiazole ring (73JHC957; 81AHC141) as in **176**. [On the basis of Korbonits's suggestion (II,B,6), however, rearrangements of Δ^2 -oxadiazolines should be more difficult, since the driving force due to amide stabilization in the final product would be lacking (83TL5763; 86JST215.) To get information on the mechanism, two approaches were explored: (a) the piperidine-catalyzed rearrangement of the unsubstituted hydrazone in different solvents [83JCS(P2)1199]; (b) the amine-catalyzed rearrangement of the

p-nitrophenylhydrazone (**171**; X = *p*-NO₂) in the presence of various amines in benzene [81JHC723; 83JCS(P2)1203].



In all the solvents used, the rearrangement of the unsubstituted phenylhydrazone follows a bimolecular reaction pathway involving one molecule of substrate and one molecule of piperidine. However, depending on the solvent, other catalyzed pathways contribute to the global reaction. In methanol one observes catalysis by methoxide anion, but not the third-order reaction (k_{III}), implying two molecules of piperidine; in dioxan and ethyl acetate, in addition to the uncatalyzed pathway (k_u) and the bimolecular one (k_{II}), the global reaction implies a small contribution by the third-order process (k_{III}). In acetonitrile, in addition to the uncatalyzed pathway, only the bimolecular catalysis (k_{II}) term is observed; at low temperature, however, a contribution from a third-order process (k_{III}) is also observed. A comparison of kinetic data show that in benzene one observes the lower absolute kinetic constants and a higher contribution from the third-order reaction (k_{III}). In ethyl acetate and dioxan, because of their nucleophilic character, higher values of absolute rate constants and similar values of the (k_{II}) and (k_{III}) terms are found. Furthermore, in methanol and acetonitrile, because of the properties of these solvents, higher values of the uncatalyzed reaction (k_u) are found.

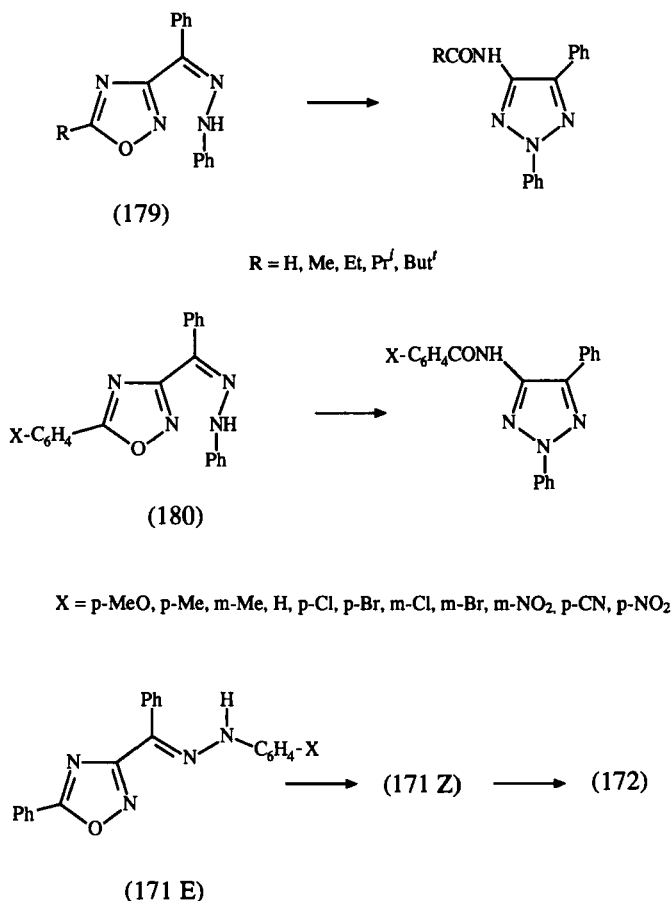
Regarding the amine-catalyzed rearrangement of the *p*-nitrophenylhydrazone [81JHC723; 83JCS(P2)1203], all the amines catalyze the reaction; nevertheless, depending on the nature of the amine, different catalysis laws are observed. Tertiary amines and secondary amines with great

steric requirements follow the reaction pathway requiring one molecule of amine, which therefore acts as a general base; secondary cyclic amines and diethylamine show a reaction pathway requiring two molecules of amine; here, the second molecule of amine serves to catalyze catalysis as in **177**. Secondary amines with intermediate steric requirements follow both reaction pathways. Catalysis by primary amines implies three molecules of amine, according to a catalysis of catalysis model as a function of the number of hydrogen atoms on the amine nitrogen, as in **178**. Furthermore, catalysis by primary diamines parallels that of primary amines, except for the possibility of an internal interaction that depends on the length of the diamine chain. Finally, catalysis by various couples of amines at different concentrations confirms the catalysis of catalysis mechanism.

Regarding electronic effects exercised by substituents as a function of solvent, the results show that in all the solvents used the reactivity of the piperidine-catalyzed reaction is increased either by electron-withdrawing or by electron-releasing substituents, but with different efficiency for each solvent. Moreover, in accordance with a polar transition state in the rearrangement, substituent effects on the global reactivity increase with increasing solvent polarity [86JCS(P2)1183].

c. Rearrangements of Z Phenylhydrazones of 3-Benzoyl-5-alkyl-(5-aryl)1,2,4-oxadiazoles. To get information on the influence of substituents at the C(5) position of the oxadiazole ring, rearrangements of *Z* phenylhydrazones of some 3-benzoyl-5-alkyl-oxadiazoles (**179**) and 3-benzoyl-5-aryl-oxadiazoles (**180**) are considered [84JCS(P2)541, 84JCS(P2)785]. As for 5-alkyl-substituted derivatives **179**, the results show that 5-alkyl substituents only weakly influence reactivity. On this ground, the postulated pathway involving addition of piperidine to the C(5)—N(4) double bond of the oxadiazole (as in **176**) in the piperidine-catalyzed rearrangement is excluded. The small variations in reactivity are attributed to the small electronic effects exercised by 5-alkyl substituents on the "leaving group ability" of the C(5)—O moiety. Accordingly, reactivity increases on going from the C(5)-methyl- to the C(5)-phenyl-substituted, and then to the 5-unsubstituted oxadiazole, this latter being the most reactive. A similar trend in reactivity is also observed for the rearrangements of some 5-substituted 1,2,4-oxadiazoles containing a reacting CCN side-chain [82JCS(P1)759] (Sections II,A,8 and II,B,6).

For the rearrangement of 5-aryl-substituted phenylhydrazones **180**, kinetic data in dioxan–water at various pS^+ show the two expected reaction pathways: uncatalyzed and base-catalyzed. Moreover, at each pS^+ , the rearrangement rate depends on the substituent in the C(5)-aryl group: electron-withdrawing substituents increase reactivity, whereas electron-



SCHEME 31

releasing ones decrease it. The Hammett correlations with σ constants are excellent in the pS^+ -independent range (at $\text{pS}^+ 3.80\text{--}6.00$, $\rho 0.847$). However, in the base-catalyzed range, the correlations are improved by the use of σ^n (at $\text{pS}^+ 10.0$, $\rho 1.72$), thus suggesting that in the transition state there is no conjugation between the *para* substituents in the C(5)-aryl ring and the leaving group C(5)—O. Considering that electronic effects are exercised by substituents which are very far from the reaction center, the observed ρ values (70M11) suggest a concerted process in the formation of the N—N bond and breaking of the O—N one; however, the transition state of the base-catalyzed reaction has a higher negative charge in the oxadiazole ring because of a larger breaking degree of the O—N bond. In the

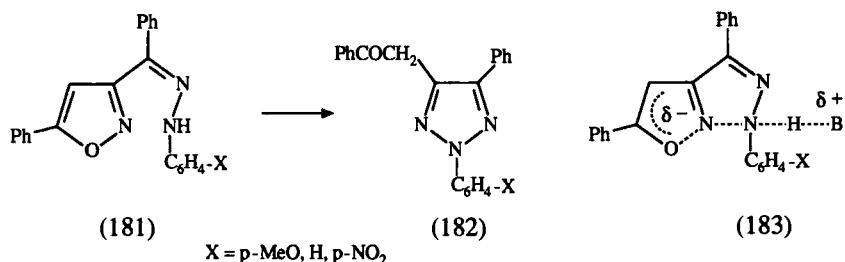
pS^+ -independent range the susceptibility constants are lower, thus suggesting a transition state with a smaller degree of breaking degree of the O—N bond. (See also Sections II,A,8 and II,B,6.)

2. *Isomerization and Rearrangement of E Arylhydrazones of 3-Benzoyl-5-phenyl-1,2,4-oxadiazoles*

The piperidine-catalyzed rearrangement of the *E* hydrazone isomer **171E** ($X = H$) into **172** ($X = H$) in benzene proceeds through a prior *E* to *Z* piperidine-catalyzed isomerization as the determining step in the global reaction (80JHC801). The piperidine-catalyzed isomerization has been extended to a series of arylhydrazones (**171E**) in different solvents (benzene, dioxan, acetonitrile) [90JCS(P2)215]. Kinetic data show that for each arylhydrazone the rate constants are little affected by the nature of the solvent; moreover, the effects of substituents on the isomerization reactivity are very low. In each solvent, the same trend in reactivity by varying the substituent is observed: a decrease of reactivity on going from the *p*-Me- to the *m*-Me- substituted or to the unsubstituted arylhydrazone; an increase up to the *p*-Cl, and then a new decrease going to the *p*-NO₂-substituted arylhydrazone, through the *m*-NO₂ and *p*-CN compounds. The Hammett plot shows a *zig-zag* trend, and this is explained by assuming a change of mechanism (rotation or imino nitrogen inversion) and/or of the rate-determining step by varying the substituent (71JCE103; 72MI1; 88MI2). An electronreleasing substituent, by increasing the nucleophilicity of the α -nitrogen atom favors the rotation mechanism. On the other hand, when a weakly electron-withdrawing substituent is present, the rate-determining step can be identified in the formation of an ionic couple between the arylhydrazone and the piperidine. Finally, when highly electron-withdrawing substituents are present, the rate-determining step can be identified in the inversion at the imino nitrogen.

3. *Rearrangements of Z Arylhydrazones of 3-Benzoyl-5-phenylisoxazole*

Qualitative results show that for a given side-chain, the rearrangement rates decrease in the order 1,2,4-oxadiazole > isoxazole > 1,2,5-oxadiazole (81AHC141). Quantitative information on reactivity are reported for some *Z* arylhydrazones of 3-benzoyl-5-phenylisoxazole (**181**) [87JCS(P2)537; 88JCS(P2)1683]. In dioxan–water and in the range of pS^+ 9.80–13.60, kinetic data show that arylhydrazones **181** rearrange into phenacyltriazoles **182** more slowly than arylhydrazones of 3-benzoyl-5-phenyloxadiazole and follow a general-base-catalyzed reaction. Kinetic



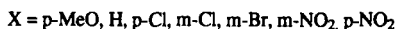
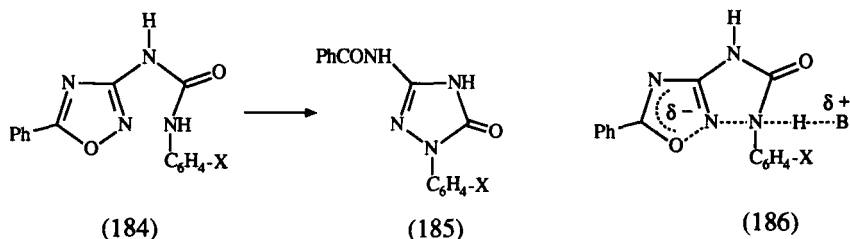
isotopic effects at various pS^+ indicate a $(k_A)\text{H}/k_A\text{D}$ ratio of about 2.8, and this suggests a proton transfer in the rate-determining step. Regarding the electronic effects of substituents, kinetic data show that either electron-withdrawing or electron-releasing groups increase the rearrangement rate compared with the unsubstituted term. These results, which parallel those observed for 1,2,4-oxadiazole arylhydrazones (see earlier), suggest the transition state **183**, in which the degree of formation and breaking of the bonds will depend on the substituent in the arylhydrazone moiety. The high activation enthalpies indicate that in reaching the transition state, the resonance stabilization of the rearranging ring is partly lost. In the amine-catalyzed rearrangement of the *p*-nitrophenylhydrazone **181** ($\text{X} = p\text{-NO}_2$) in benzene, the reaction rate is highly dependent on the amine concentration; moreover, as already observed in the 1,2,4-oxadiazole series, the reactivity and the type of catalysis depend on the nature of the amine as catalyst [88JCS(P2)1683].

Comparing the reactivity of isoxazole arylhydrazones and that of structurally related 1,2,4-oxadiazole arylhydrazones, much lower kinetic constants are observed for isoxazole substrates ($k_A \text{ oxadiazole}/k_A \text{ isoxazole} > 10^3$). This trend in reactivity is explained either by the different O—N bond strength or by the different nucleofugacity of the leaving-group in the rearranging heterocycles. The aromatic character and the π bond order of the O—N bond are lower in the oxadiazole ring (67TCA342; 68T485; 70BCJ3344). Moreover, the NCO leaving-group (oxadiazole), compared with the CCO group (isoxazole), should favor rearrangements in the 1,2,4-oxadiazole series because of its greater ability to stabilize the negative charge resulting in the reaction.

4. Rearrangements of *N*-Aryl-*N'*-(5-phenyl-1,2,4-oxadiazol-3-yl) ureas

The base-catalyzed rearrangement of oxadiazolylureas **184** into benzoylamino-1,2,4-triazolin-5-ones **185** has been mechanistically examined by using amines as catalysts in acetonitrile and benzene, and borate buffers at various pS^+ in dioxan–water [90JCS(P2)1289]. For the piperidine-

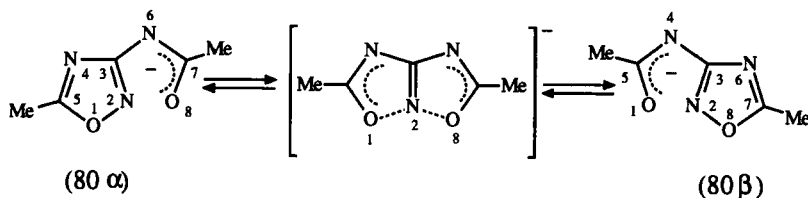
catalyzed reaction the results indicate a single reaction pathway involving one molecule of amine; moreover, substituents in the aryl moiety largely influence reactivity, and an excellent linear free-energy correlation (ρ 2.45) is observed. A comparison between the two reacting side-chains (CNN and NCN, respectively) shows that arylhydrazones rearrange faster than arylureas and that ratios of rate constants decrease with an increase in acidity of the ArN—H group of the arylureas. In contrast to the piperidine-catalyzed rearrangement of the *Z* arylhydrazones in dioxan [86JCS(P2)1183], the free energy plot is linear, thus suggesting that the structure **186** for the transition state is not substituent-dependent. This result agrees with the much lower nucleophilicity of the attacking nitrogen and the higher acidity of the ArN—H group of arylureas compared with *Z* arylhydrazones. In the piperidine-catalyzed rearrangement of arylureas, no matter what the substituent is, the reactivity will depend on the breaking degree of the N—H bond.



As for the rearrangement in dioxan–water in the presence of borate buffers, the reactivity of all the substrates shows a limiting rate constant at a given high pS^+ value, which is different for each aryl group. This behavior differs from that observed for arylhydrazones and suggests a reaction mechanism involving specific-base catalysis. At high pS^+ , the acidity of the N—H group allows the formation of the conjugated base, which will slowly rearrange. Concerning the effect of substituents in the arylurea moiety, excellent linear correlations are obtained. However, as expected on the basis of the mechanism, susceptibility constants are higher in the pS^+ -dependent range (where a fast acid–base equilibrium occurs) than in the pS^+ -independent one (where the anionic substrate slowly rearranges). Activation parameters agree with an S_Ni -type reaction with a highly solvated transition state, the formation of which couples with the partial loss of the stabilization energy of the starting oxadiazole. The lower reactivity of arylureas with respect to arylhydrazones seems essentially dependent on the enthalpy factor, and this is also related to the different stabilization of the two final rings.

5. Rearrangement of 3-Acylamino-1,2,4-oxadiazoles

For the fully-degenerate rearrangement $80\alpha \rightleftharpoons 80\beta$, a value of the free energy of activation, ΔG^\ddagger , of 19.6 kcal mol⁻¹ results from a dynamic ¹H-NMR method using DMSO (75JHC1327; 81AHC141). Some information about the transition state is drawn from theoretical calculations at the



SCHEME 32

MNDO and AM1 level (91H1547). Assuming as an arbitrary coordinate the length of the O(1)—N(2) bond that is breaking, the resulting transition state shows an *unsymmetrical* arrangement; that is, the length of the N(2)—O(8) bond that is forming is higher than the O(1)—N(2) bond that is breaking. The calculated ΔE (71.6 kcal mol⁻¹ at MNDO level) greatly differs from the experimental free energy of activation obtained by the coalescence method. This discrepancy is ascribed mainly to the dipolar aprotic solvent, which strongly favors the interconversion of the anionic species. For the equilibrium $81 \rightleftharpoons 82$, exploiting the difference in frequency between the methyl signals in the NMR spectra in DMSO, an experimental value of $\Delta G^\ddagger = 27$ kcal mol⁻¹ was calculated. This value is higher than that found experimentally for the equilibrium in the anion **80** and this is in line with the expected lower reactivity of a neutral side-chain.

6. Rearrangements Involving a Side-Chain CCN in the 1,2,4-Oxadiazole Series

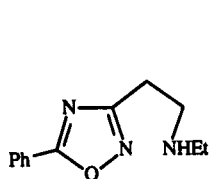
For rearrangements of oxadiazoles **131**, kinetic data suggest a concerted mechanism with a polar transition state, or an anionic mechanism, this latter for the base-promoted reactions in substrates having an acid N—H group [82JCS(P1)759]. Electronic effects of substituents in the C(5)-aryl group in the thermally induced rearrangement of **131** (R = *p*-XC₆H₄) support a good Hammet correlation with a ρ value (0.89) essentially identical to that calculated for the rearrangement of phenylhydrazones of 3-benzoyl-5-aryl-1,2,4-oxadiazoles ($\rho = 0.847$) in the pS⁺-independent range. Analo-

gously, the reactivity increase on going from the 5-alkyl derivatives (**131**; R = alkyl) to the 5-phenyl-substituted substrates (**131**; R = phenyl) is essentially due to the electronic effects on leaving-group ability; this parallels that observed for the rearrangement of phenylhydrazones of 5-alkyl- or 5-phenyl-oxadiazoles (Section II,B,1). In reaching the transition state, the determining role of the π electronic system of the oxadiazole ring is emphasized. In support, some comparative evaluations of the reactivity of a saturated and an unsaturated side-chain are reported. Calorimetric analysis shows comparable results in the rearrangement of compounds **187** and **188**: in both cases the driving force of the exothermic reaction resides in the thermodynamic stability of the rearranged product, which is amidic in nature [82JCS(P1)759]. Kinetic data on the rearrangement of **127** and **145** show comparable ρ values, thus indicating that the π -electronic system of the oxadiazole moiety must play a determining role in both reactions; by contrast, the saturated or unsaturated side-chain should play no part either in feasibility or in mechanism. Thus, the extended scheme **191** \rightarrow **192** is pictured, by which the azole-to-azoline rearrangements are systematized [82JCS(P1)759; 86JCS(P1)9]. In line with the determining role exercised by the conjugation in the starting ring, it is claimed that Δ^2 -oxadiazolines **189** and **190** do not rearrange under those conditions used to rearrange the corresponding oxadiazoles (83TL5763). As further support, theoretical calculations show the presumed rearrangement of oxadiazoline **193** to be highly endothermic, whereas rearrangements of oxadiazoles **194** and **195** are exothermic (86JST215).

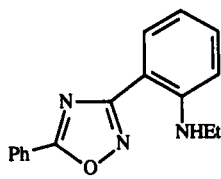
C. REARRANGEMENTS INVOLVING CLEAVAGE OF AN N—N BOND

Rearrangements of 1,2,3-triazoles **196** (74MI1), benzotriazoles **197** (78HCA2628), or tetrahydrobenzotriazoles **198** (R = H) (86JHC443), which imply the cleavage of an N—N bond, do not occur either by thermal or by photochemical pathways. Moreover, for some tetrahydrobenzotriazoles (**198**; R = Me; Ar' = Ph) analysis of fragmentation pattern at 70 eV shows that the rearrangement also does not occur under electronic impact conditions (86JHC443).

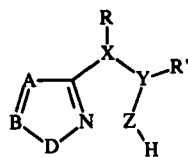
Thermolysis of 5-azido-1,2,3-triazoles **199** into diazotetrazoles **201** (83BSB913; 85T4621; 88T3617; 89BSB421, 89T749; 90BSB213) can be included, at least formally, in this class of rearrangements. In fact, they are interpreted via an N—N bond cleavage and a subsequent heterocyclization at a nitrogen atom as the pivotal center by a three-atoms side chain (the azido group). Diazotetrazoles **201** can be isolated as such, or can undergo further reactions. The rearrangement strongly depends on the



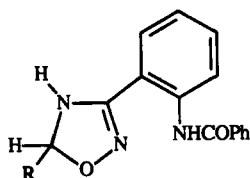
(187)



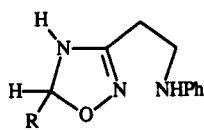
(188)



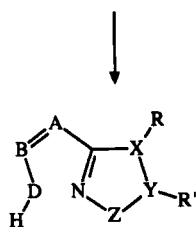
(191)



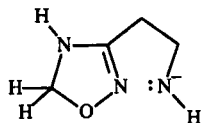
(189)



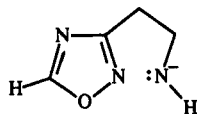
(190)



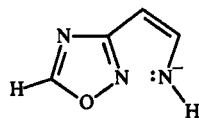
(192)



(193)

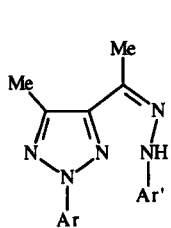


(194)

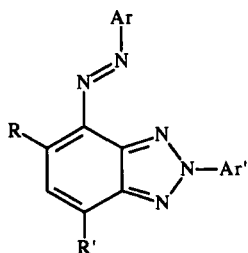


(195)

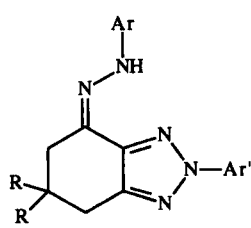
nature of substituents at the C(4) position of the triazole ring and proceeds only when strongly electron-withdrawing groups are present. Different structural patterns direct the thermolysis to produce triazenes and nitrogen. Kinetic studies varying the Ar group show that electron-withdrawing substituents at N(1) provide an increase in reaction rate, which also increases as the solvent polarity decreases. Thermolysis in benzene or in a



(196)



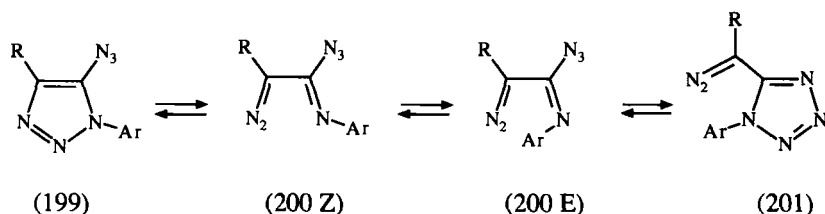
(197)



(198)

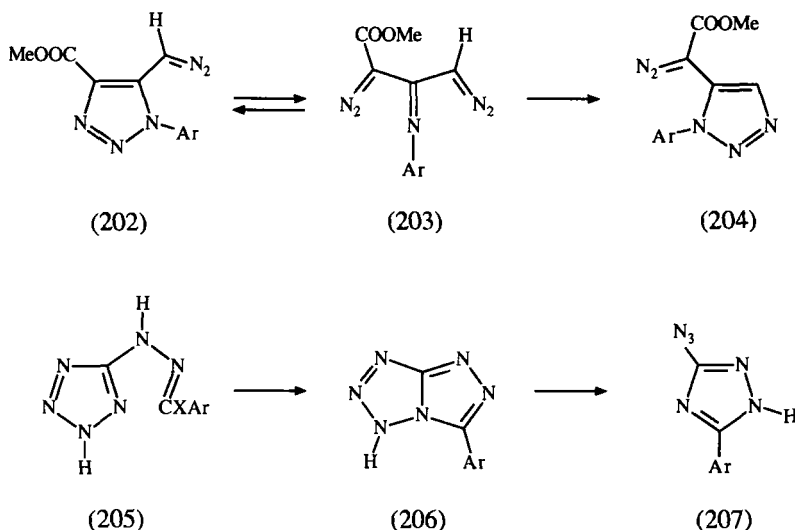
nitrile solution also gives insertion of the solvent into the carbene species arising from diazo compound **201**. Furthermore, when R is a $\text{CH}=\text{NR}'$ system, a subsequent heterocyclization involving the diazo group and the insaturated substituent itself can also arise from the initially rearranged tetrazoles. Mechanistically, the reversible ring opening of the azidotriazoles into Z azido-imino intermediates **200Z** is the rate-determining step; the subsequent configurational isomerization at the imino moiety, and then the reversible ring closure of the azido-imino species having the correct configuration, would give rearranged tetrazoles **201** (Scheme 33).

Isoheterocyclic (ring-degenerate) rearrangements are also known in this series (88T461). A ring opening of the 5-diazomethyltriazoles **202** into **203**, followed by heterocyclization involving the three-atoms side group



Ar = Ph, p-MeC₆H₄, p-ClC₆H₄, p-NO₂C₆H₄, 4-Pyridyl, 1-Naphthyl

R = COOMe, CHO, PO(OEt)₂, SO₂Ph, CN, $\text{CH}=\text{NR}'$



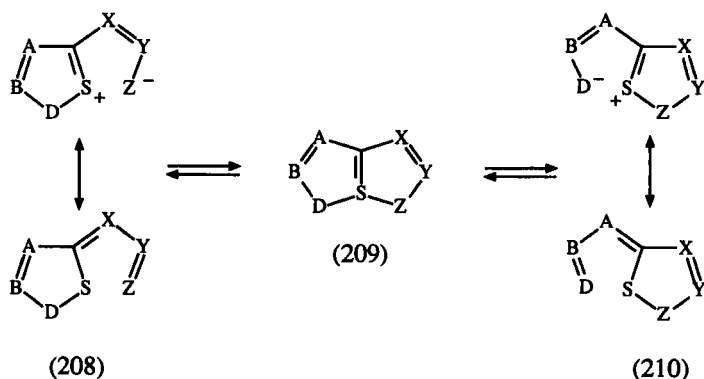
SCHEME 33

$\text{CH}=\text{N}_2$ leads to the ring-degenerate rearrangement into triazoles **204** (Scheme 33). The occurrence of this rearrangement is highly dependent on the nature of the substituents. In fact, the 1,4-diphenyl-5-diazomethyltriazole does not rearrange; moreover, the reaction proceeds only when strongly electron-withdrawing groups (e.g., nitrophenyl or dinitrophenyl) are bound at the N(1) of the triazole (88T461), and the driving force stays in the carboxymethyl-stabilized diazo group in the rearranged product. Different rearrangements proceeding via diazoimine intermediates regard heterocyclizations involving side-chains linked at C(4) of the triazole ring (90BSB281, 90BSB833, 90JHC2021).

The base-promoted transformation of hydrazonoyltetrazoles **205** into 3-azidotriazoles **207** does not fit our general scheme; the reaction is explainable by the triazolo-tetrazole intermediate **206**, arising from a nucleophilic attack of the annular nitrogen on the azacarbonium ion of the side-chain. In the subsequent azidotetrazole tautomerism, the azidotriazole species **207** is favored by the electron-withdrawing character of the triazole ring [71JCS(C)2769, 74JOC1522; 77AHC323].

III. Rearrangements Involving the Pivotal Sulfur Atom in the Starting Ring

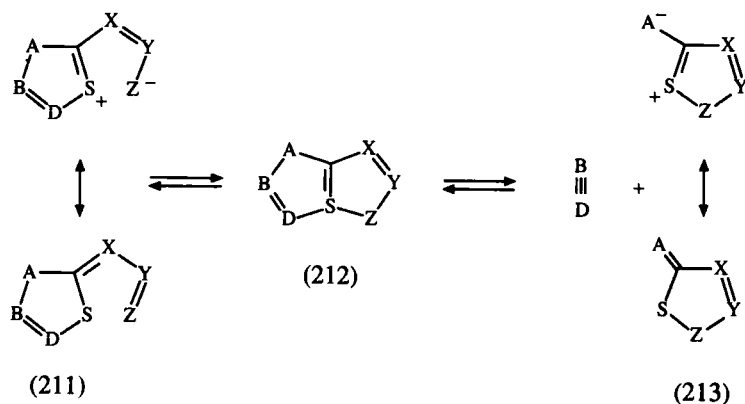
Rearrangements involving the sulfur atom as the pivotal center in the starting heterocycle and a nucleophilic three-atoms side-chain can be generalized according to Scheme 34, which demands a displacement at sulfur via a heterothiapentalene-type intermediate (**209**). Reversible bond-switches at the hypervalent sulfur have been also considered. Much evidence suggests that to some extent interactions exist between atoms $\text{Z}\cdots\text{S}$ and $\text{D}\cdots\text{S}$ of the starting and the rearranged species. (**208**) and (**210**),



SCHEME 34

respectively. Moreover, here is a borderline of no bond resonance compounds (71AHC161; 72MI2; 80MI2). In fact, the starting and final structures of a rearrangement equation, could also represent canonical forms of the thiapentalene-type intermediate (72MI2).

Unlike the O—N-bond-containing heterocycles, the pivotal sulfur-containing systems can also rearrange by elimination of a small species, according to the generalized pathway **211** \rightarrow **213** (Scheme 35). The reverse



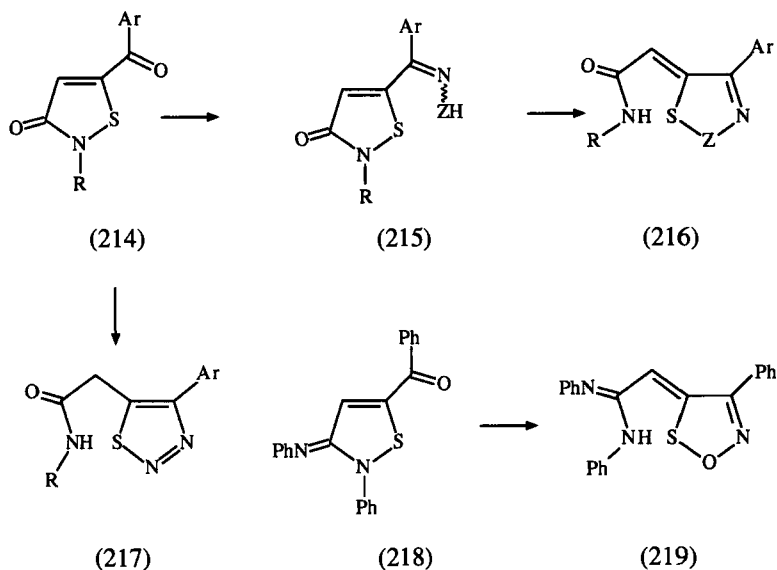
SCHEME 35

reaction, which is a cycloaddition–rearrangement, is also extensively documented; substrate **213**, which has a dipolar reactivity because of the electron-donor character of sulfur, will react with dipolarophile $B \equiv D$ to give the rearranged **211**. Indeed, the common intermediate **212**, at least formally, could justify both the direct and the reverse process. Interesting and significant results in this area are reported by Japanese (Akiba) and Belgian (L'abbé) groups. For greater convenience, this chapter will be subdivided taking into account the bond that is cleaved in the rearrangement, namely the N—S or S—S bond, and the number of heteroatoms in the rearranging ring. As far as the cycloaddition–rearrangement reactions are concerned, only representative examples will be discussed.

A. REARRANGEMENTS INVOLVING CLEAVAGE OF AN N—S BOND

1. Isothiazoles

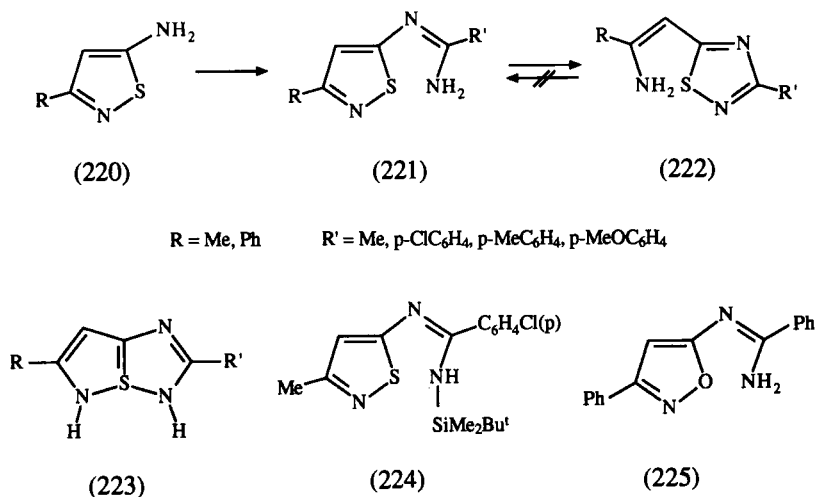
The reaction of 2-substituted-5-aryl-isothiazol-3-ones (**214**) with hydroxylamine or arylhydrazines gives the 1,2,5-oxathiazoles **216** ($Z = O$) or 1,2,3-thiadiazoles **216** ($Z = NAr'$), as a result of a spontaneous rearrangement of unisolated oximes **215** ($Z = O$) or arylhydrazones **215**



SCHEME 36

(Z = Nar'), respectively (Scheme 36). Considering that the rearrangement proceeds more easily and with better yields by having the reagents in the presence of acids (acetic or sulfuric acid), the displacement at sulfur by the side-chain (the Z atom) is suggested to take place on the protonated isothiazole ring (84JHC1679). In this way, compounds **214** and semicarbazide produce thiadiazoles **217**, resulting from the fragmentation of the initially formed thiadiazoles **216** (Z = NCONH₂); on the other hand, the rearranged **217** (Ar = Ph; R = PhCH₂) is also reached from the corresponding **214** and hydrazine in acetic acid. By similar behavior, the 5-benzoyl-3-phenylimino derivative **218** reacts with hydroxylamine to give directly the rearranged oxathiazole **219** (Scheme 36) (84JHC1679). Such rearrangements, involving the O—N bond however, are familiar and widely proved reactions for 3-acyl-1,2,4-oxadiazoles, 3-acylisoxazoles, and 3-acyl-1,2,5-oxadiazoles (Sections II,A,1 and II,A,2).

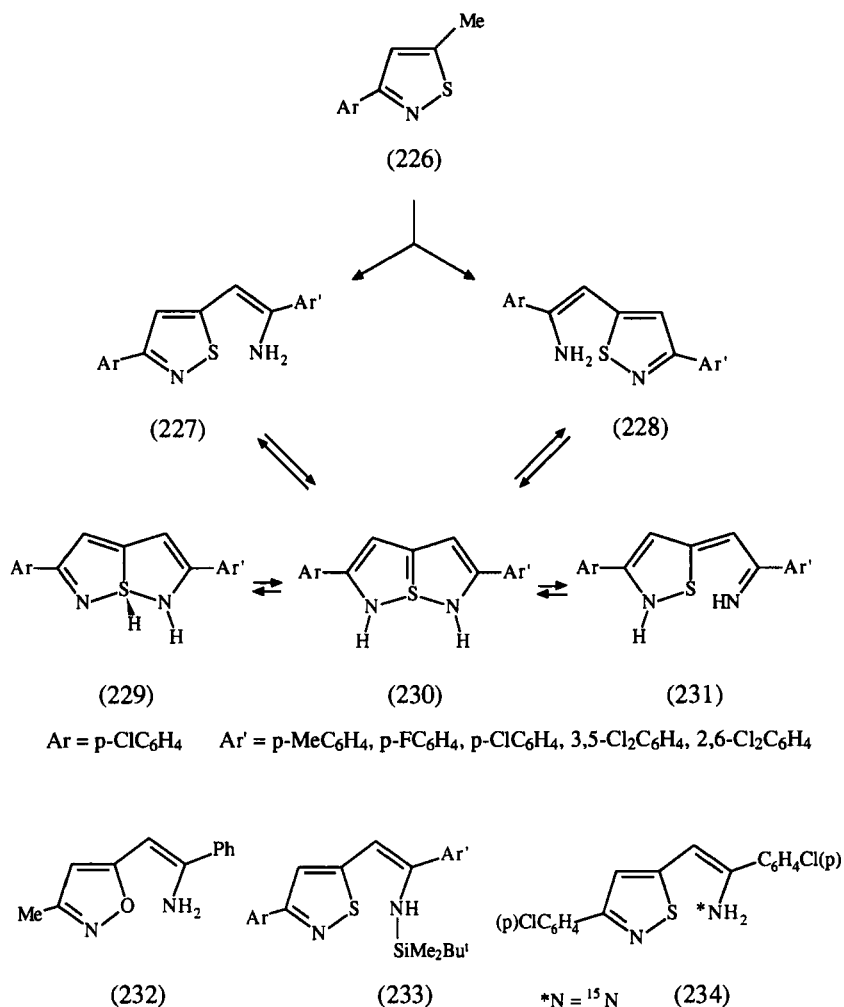
The reactivity of 5-amidinoisothiazoles (**221**) was explored to demonstrate the equilibrium **221** \rightleftharpoons **222** (Scheme 37). However, on reacting with nitriles or imidates, 5-amino compounds **220** (R = Me, Ph) give directly the rearranged thiadiazoles **222**. The equilibrium between the two heterocycles (in different solvents at room temperature) is not observed, and this result is attributed to the greater stability of the 1,2,4-thiadiazole



SCHEME 37

heterocycle with respect to the isothiazole one (81H1155; 83PS111). Moreover, the spontaneous isothiazole-to-thiadiazole rearrangement takes place even in the desilylation of **224** at -78°C in THF (84TL4561). For the observed rearrangement, the determining role is exercised by the intermediacy of the sulfurane species **223**; in support of this suggestion it is emphasized that the related 5-amidinoisoxazole **225** does not give an equivalent rearrangement where the oxygen would act as the pivotal center (in an unlikely reverse breaking of the O—N bond, however) (83PS111).

Isoheterocyclic rearrangements, also fully degenerate, are indicated for 5-(2-aminovinyl)isothiazoles **227** (Scheme 38). In the synthesis of these compounds starting from 3-aryl-5-methylisothiazoles (**226**), both isomers **227** and **228** are directly obtained, and in the equilibrium between them the determining participation of sulfurane **230** is emphasized. Again, it is reminded that the related 5-aminovinylisoxazole **232** does not rearrange (73BCJ3533; 84TL4561). The equilibrium $\mathbf{227} \rightleftharpoons \mathbf{228}$ was explored by ^1H -NMR techniques starting from pure components **227** having the correct *Z* geometry, which in turn are obtained by desilylation of **233**. The reversible rearrangement takes place in neutral medium (benzene or DMSO), or in the presence of acid or base catalysis (in DMSO containing pyridinium hydrogen tetrafluoroborate or pyridine, respectively). Moreover, the fully degenerated process on **227** ($\text{Ar} = \text{Ar}^1 = p\text{-ClC}_6\text{H}_4$) is verified by utilizing the ^{15}N -labeled isomer **234**. The most significant results from the mechanistic studies indicate that (84TL4561; 85JA2721) (a) the equilibration is a monomolecular reaction and follows reversible first order kinetics; (b) the

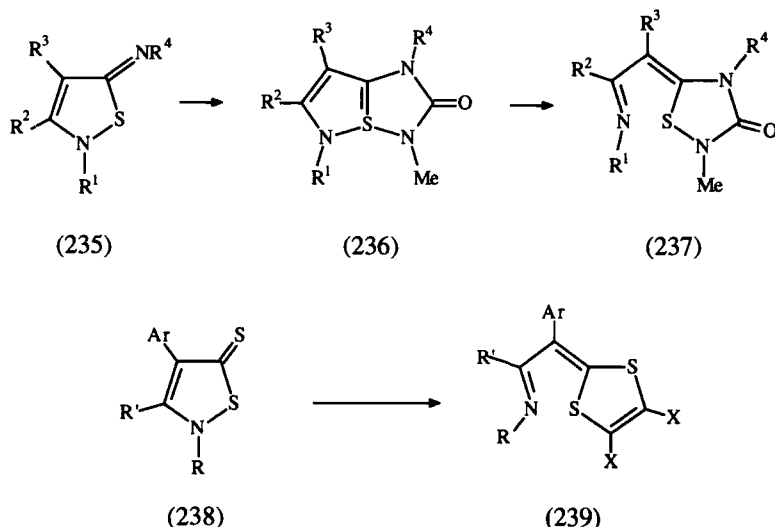


SCHEME 38

reaction is highly accelerated either by acid or base catalysis (protonation of the isothiazole nitrogen favors the cleavage of the N—S bond, whereas base catalysis enhances the nucleophilicity of the attacking nitrogen of the side-chain) and in both catalyzed reactions, the process implies the intermediacy of sulfurane **230**; (c) in the absence of catalysis, the equilibrium reaction is faster in a nonpolar solvent (benzene) than in DMSO, and that indicates a nonpolar transition state and a ground state where the amino group is highly solvated in DMSO. For the uncatalyzed re-

arrangement, rather than an S_N2 type of transition state involving a zwitterionic species, the sulfurane **230** is equally suggested as a key intermediate. In this case, however, this species should be reached by sigmatropic shifts involving **229** or **231** as precursors (Scheme 38) (85JA2721). For the uncatalyzed fully degenerate reaction, a free energy of activation, ΔG^\ddagger , of 24.4 kcal mol⁻¹ (in benzene-*d*₆ at 25°C) is calculated. Moreover, typical ΔG^\ddagger values in the equilibration of compound **227** (Ar = *p*-ClC₆H₄; Ar' = 3,5-Cl₂C₆H₃), extrapolated to 25°C, were 24.1 kcal mol⁻¹ (in benzene-*d*₆) and 25.1 kcal mol⁻¹ (in DMSO-*d*₆).

According to the generalized pattern, which provides rearrangements from a cycloaddition reaction, iminoisothiazoles **235** react with methyl isocyanate to afford directly the rearranged **237**, probably via intermediates **236** (Scheme 39) (77CB285). Similar cycloaddition-rearrangements occur on reacting compounds **235** with carbon dioxide or carbon disulfide (77CB285). By a similar pathway, isothiazole-5-thiones **238** react with activated acetylenes to rearrange into corresponding 1,3-dithioles **239** (Scheme 39) [74CJC1738; 80JCS(P1)2693].



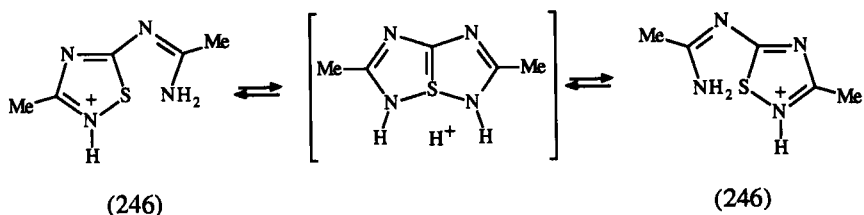
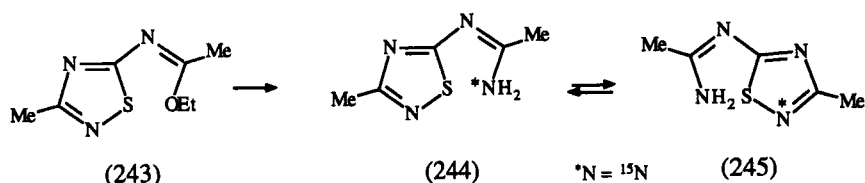
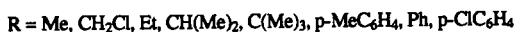
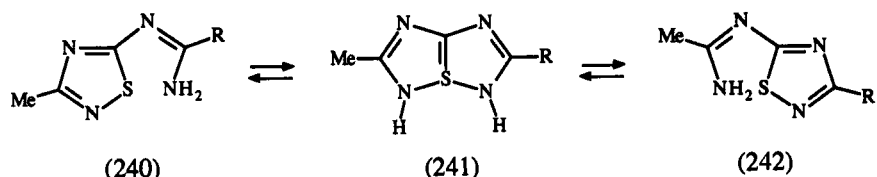
SCHEME 39

2. 1,2,4-Thiadiazoles

Some typical rearrangements in this series have been reviewed in a different context, concerning 1,2,4-thiadiazole chemistry [82AHC(32)285].

5-Amidinothiadiazoles **240**, obtainable from the 5-amino-3-methyl-1,2,4-

thiadiazole and nitriles (RCN) in the presence of AlCl_3 , equilibrate with thiadiazole isomers **242** via the participation of thiapentalene-type intermediates **241** (Scheme 40) (79JA5857). The equilibrium position depends on



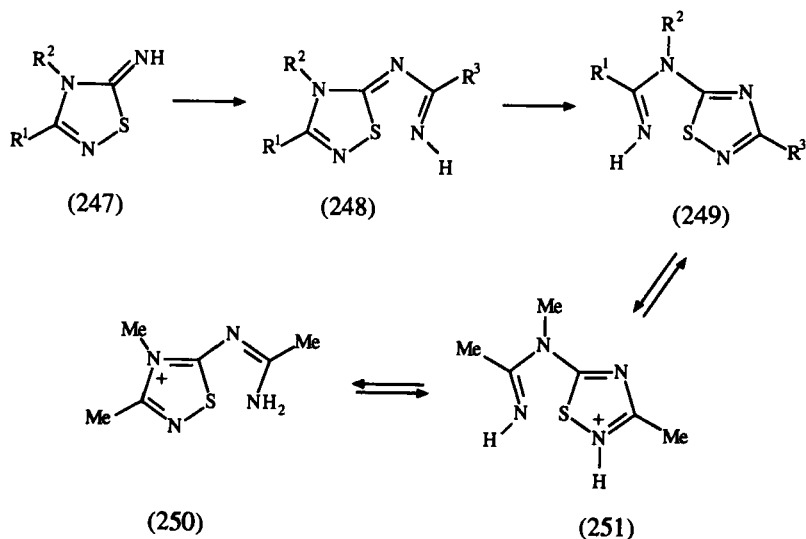
SCHEME 40

the solvent and on the nature of R: in chloroform at 34°C , bulky alkyl groups or an aryl bearing electron-withdrawing substituent favors the thiadiazole isomer **242** having R linked at the ring. Moreover, the thiadiazole isomer **242** ($\text{R} = \text{CH}_2\text{Cl}$) predominates in polar solvents (acetone, DMSO, methanol) (79JA5857). Again, in support of the determining participation of a hypervalent sulfur in the rearrangement, it is emphasized that structurally related 5-amidino-1,2,4-oxadiazoles do not rearrange (79JA5857).

In the case of the thiadiazole **240** ($\text{R} = \text{Me}$), the occurrence of a bond-switch is verified by ^{15}N -labeling experiments. Thus, the reaction between the imidate **243** and $^{15}\text{NH}_3$ gives a mixture of both thiadiazoles **244** and **245**, which are characterized by ^{15}N in the amidine side-chain or in the

heteroring, respectively (Scheme 40) (89BCJ479). On the other hand, the fully degenerate rearrangement is demonstrated by dynamic ^1H -NMR and shown to occur in the presence of either bases (87BSB827) or acids (84JA2713; 89BCJ479). At room temperature, the ^1H -NMR spectrum of thiadiazole **240** ($\text{R} = \text{Me}$) in DMSO shows two methyl signals that do not coalesce up to 170°C . In the presence of equimolar amounts of potassium *t*-butoxide, the two signals coalesce even at 25°C , thus suggesting a fast equilibrium in the anion. In the presence of catalytic amounts of base, the well-distinguishable signals at room temperature coalesce at 90°C , allowing calculation of the free energy of activation, ΔG^\ddagger , of $17.7 \text{ kcal mol}^{-1}$ for the degenerate rearrangement, for which a pathway via a symmetric species is suggested (87BSB827). The bond-switch is very fast also in the presence of trifluoroacetic acid, even at room temperature. By lineshape analysis of the methyl signals, the thermodynamic parameters of the rearrangement as a function of the solvent and of the acid/substrate molar ratio can be determined. In deuteriomethanol and in the presence of at least one equivalent of trifluoroacetic acid, kinetic data indicate a free energy of activation, ΔG^\ddagger_{273} , of $14.8 \text{ kcal mol}^{-1}$, which is almost constant on increasing the acid/substrate molar ratio or on varying the solvent polarity (89BCJ479). Although the initial protonation should take place at the amidine nitrogen as the more basic site, the immediate precursor of the bond-switch should be a species protonated at N(2) of the ring, such as **246**, which should favor the displacement at sulfur by weakening the N—S bond. After taking into account the preequilibrium protonation at the amidine site, a value of ΔG^\ddagger_{273} of about $8.0\text{--}10.3 \text{ kcal mol}^{-1}$ is extrapolated for the actual degenerate rearrangement of species **246**. This low barrier is attributed to the stability of a sulfurane-type intermediate (or transition state) and to the weakness of the N—S—N bonds. On the other hand, estimation of the N—S bond length suggests a “pendular movement of the central sulfur” along the rearrangement process (“bond-switching”) (84JA2713; 89BCJ479).

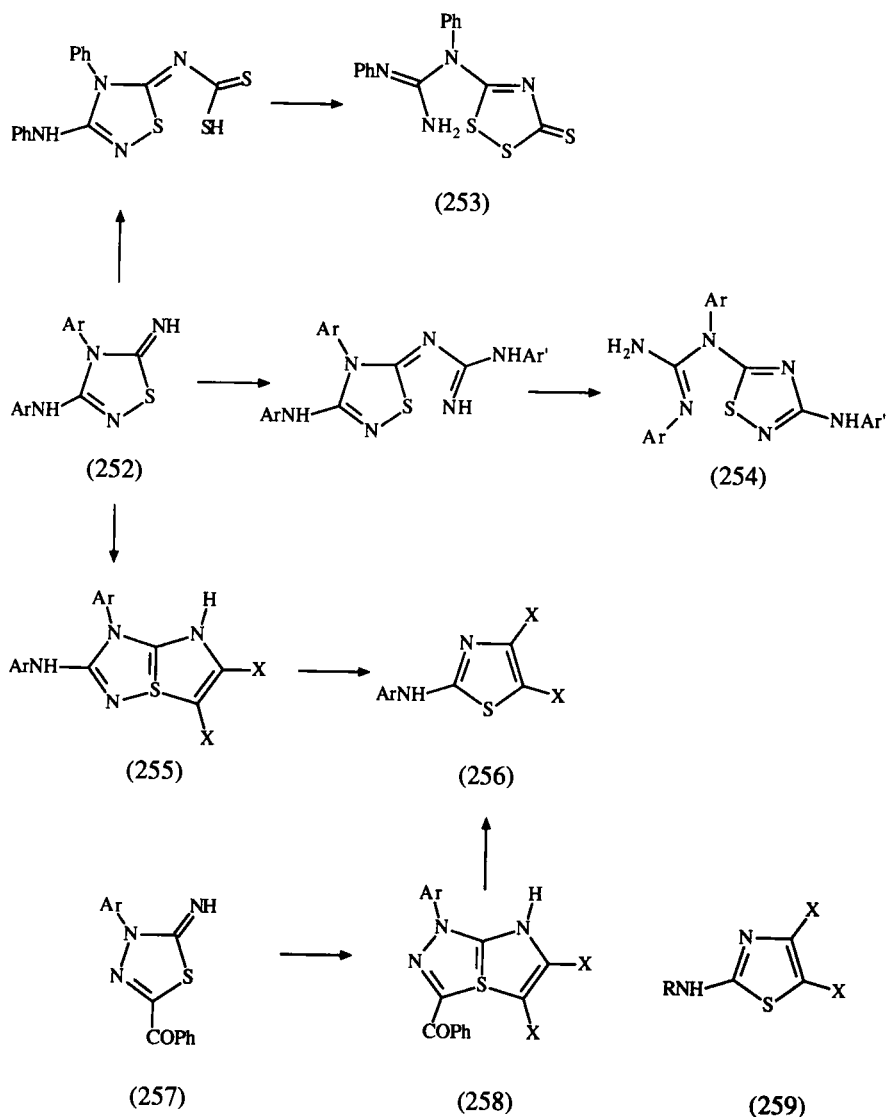
Some rearrangements in the Δ^2 -1,2,4-thiadiazoline series are explainable by a displacement at the sulfur atom. The reaction between 5-iminothiadiazolines **247** and imidates (at $60\text{--}80^\circ\text{C}$ without solvent) gives directly the thiadiazoles **249** as rearrangement products of the unisolated amidines **248** (Scheme 41). An X-ray analysis on **249** ($\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me}$), besides confirming the thiadiazole structure, suggests some coplanarity between the thiadiazole and the side-chain, as well as an intramolecular interaction between the side-chain nitrogen and the annular sulfur atoms [79AG(E)166; 81AX(B)180]. In the presence of acids (HBF_4 or TFA), the reverse process is also possible. In fact, acidification of thiadiazole **249** ($\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me}$) furnishes a protonated species for which NMR anal-



SCHEME 41

ysis indicates structure **250**, which would arise from the initially protonated thiadiazole **251** via an equilibrium implying a thiatetraazapentalenium salt (Scheme 41) [79AG(E)166]. An analogous process is observed also in the alkylation of **249**, which occurs equally at N(2) of the thiadiazole ring (78TL4117). Crystallographic analysis confirms the assigned structures [81AX(B)180].

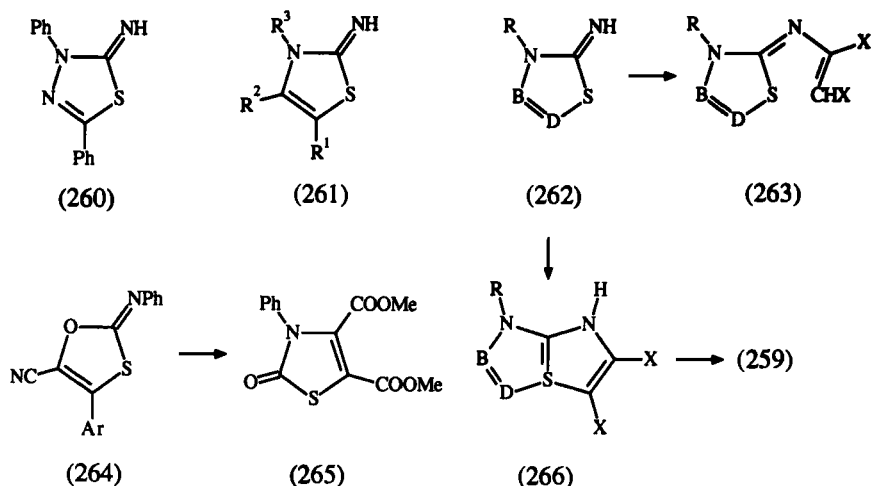
On reacting with unsaturated reagents, 5-iminothiadiazolines **252** give rearrangements involving N—S bond fission (Scheme 42). Thus, the imino **252** (Ar = Ph) reacts with carbon disulfide to give directly the dithiazole **253** (84MI2). Similarly, arylcyanamides produce compounds **254**, the structure of which is supported by an X-ray analysis (for Ar = Ar¹ = *p*-BrC₆H₄) (76CL723) that allowed the exclusion of the previously reported bicyclic isomer (75TL455). Imino compounds **252** undergo rearrangements also on reacting with activated alkynes; here, the initial 1,3-dipolar cycloaddition is followed by cleavage of an N—S bond in a sulfurane intermediate with subsequent elimination. In this way, compounds **252** (Ar = Ph, *p*-MeC₆H₄) give arylaminothiazoles **256**, arylcyanamide being eliminated from **255** (75TL459), and 5-imino-3-methyl-4-alkyl-thiadiazolines furnish alkylaminothiazoles **259** and acetonitrile (76TL1877). A related behavior involves a reaction of imino-1,3,4-thiadiazolines **257** and activated acetylenes. In this case cycloadducts **258** collapse to arylaminothiazoles **256** by cleavage of a C—S bond and extrusion of PhCOCN. As a competitive reaction, favored by polar solvents, imino compounds



SCHEME 42

257 and alkynes also give addition products (89BCJ211). On the other hand, addition but no rearrangement products are obtained in a reaction between the imino-1,3,4-thiadiazoline **260** or iminothiazolines **261** with activated acetylenes. Generally, in the reaction of imino compounds **262** with activated acetylenes, rearrangement into thiazoles **259** via **266** is

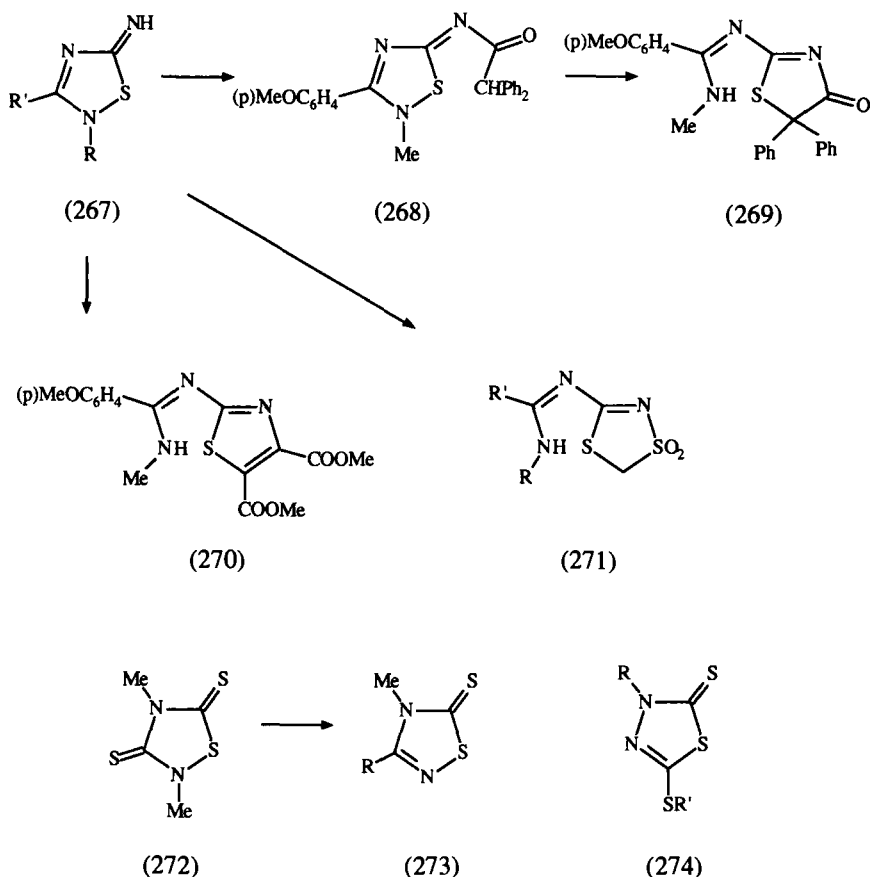
avored by the electron-withdrawing character of the heterocycle and by the high tendency to cleave of the D—S bond in **266** (89BCJ211) over competitive addition to give **263** (Scheme 43). Accordingly, phenylimino-



SCHEME 43

nooxathiazoles **264** react with dimethyl acetylenedicarboxylate to produce the rearranged 2-oxothiazole **265** (Scheme 43) (76CC912). In this case, cleavage of the C—S bond in the cycloadduct is highly favored by the presence of the CN group and by the electronegativity of the oxygen atom.

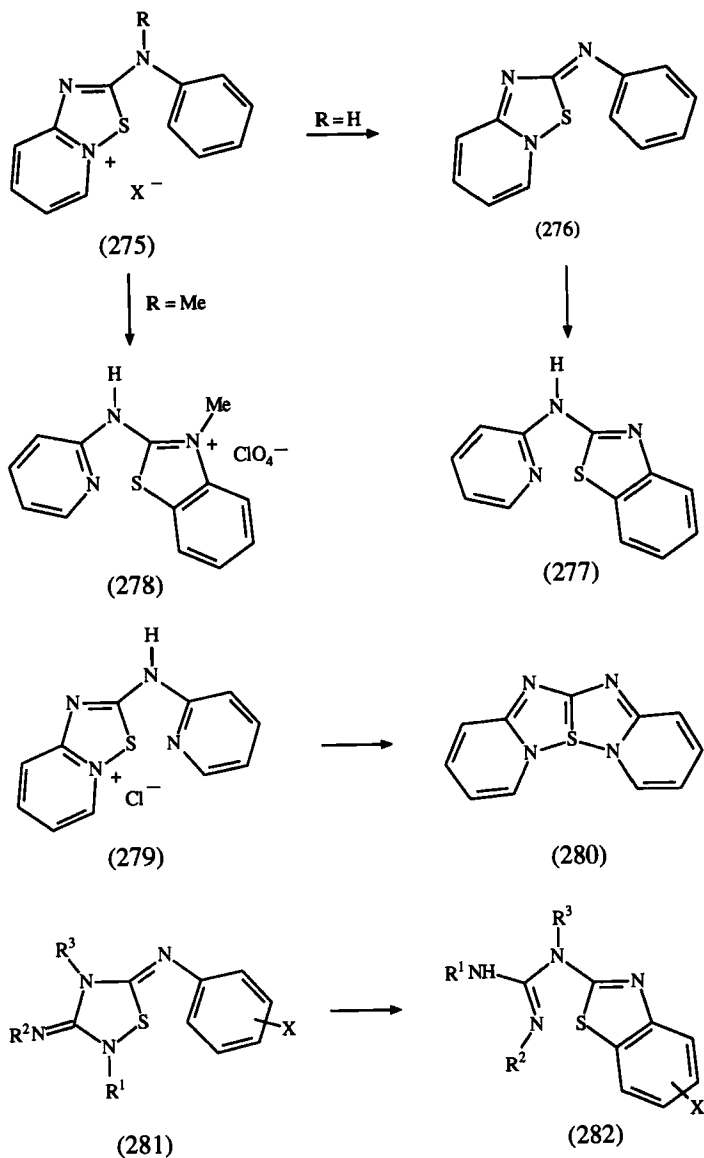
Other rearrangements pertain to 5-imino- Δ^3 -1,2,4-thiadiazolines (Scheme 44). The reaction of the imino compound **267** ($R = \text{Me}$; $R' = p\text{-MeOC}_6\text{H}_4$) as its hydrochloride with diphenylketene in pyridine at room temperature gives the acylimino derivative **268**. On warming in a polar solvent such as pyridine or acetonitrile, this compound rearranges into the thiazolin-4-one **269**, the structure of which (zwitterionic in nature) is supported by X-ray analysis (81JHC1309). The same imino compound **267** ($R = \text{Me}$; $R' = p\text{-MeOC}_6\text{H}_4$) as free base reacts with dimethyl acetylenedicarboxylate to yield the thiazole **270** directly. Furthermore, imino compounds **267** react with methanesulfonylchloride in tetrahydrofuran in the presence of triethylamine, to afford dithiazoline-4,4-dioxides **271**. Here, apart from other possible routes, a rearrangement pattern involving the carbon atom of the initially formed side-chain can be recognized (81JHC1309). Cycloaddition–elimination reactions involving the dipolar S=C=S moiety take place in thiadiazolidine-5-thione **272**. Here, the reaction with electrophilic nitriles produces thiadiazole-5-thiones **273**



SCHEME 44

($R = \text{CCl}_3, \text{COOEt}, p\text{-MeC}_6\text{H}_4\text{SO}_2$) as a result of two consecutive cycloaddition–elimination processes via thiapentalene-like intermediates, methyl isothiocyanate being the extruded species (Scheme 44) (91JOC3268). (See also Sections III,A,4 and III,B,1.) A similar cycloaddition–elimination pathway also occurs in the reaction of Δ^4 -1,3,4-thiadiazoline-2-thiones (**274**) with benzyne (76BSF120) or activated alkynes (73BSF270), where a C—S bond is cleaved and a thiocyanate species is extruded.

A special rearrangement in the 1,2,4-thiadiazole series concerns the 2-phenylamino-1,2,4-thiadiazolo [2,3,-*a*]pyridinium salts (**275**; $R = \text{H}, \text{Me}$), which are obtained by oxidation of *N*-(2-pyridyl)thioureas (Scheme 45). In the case of the unsubstituted derivative (**275**; $R = \text{H}$; $X = \text{Br}$), neutralization with sodium acetate in ethanol produces directly benzothiazole **277**



SCHEME 45

in almost quantitative yields. Evidence of the unisolated free base (**276**) is found by spectroscopic methods: addition of triethylamine to the salt solution in chloroform causes the appearance of an absorption at 380 nm (due to the intermediate base), which turns into an absorption at 313 nm,

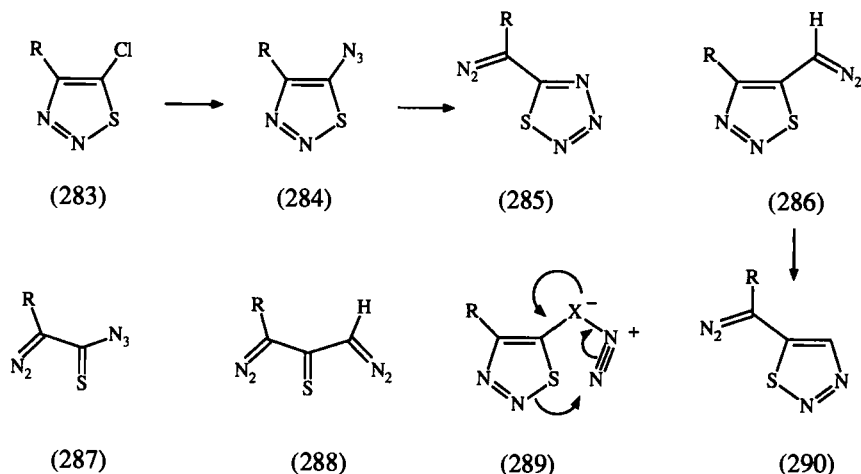
due to the rearranged product (72AJC993). The rearrangement does not depend on the presence of the free base. In fact, the *N*-methyl-substituted derivative (**275**; R = Me; X = ClO₄) rapidly rearranges into the benzo-thiazolium salt **278** either in solution or in the solid state. In both cases, the rearrangement follows first-order kinetics. Interestingly, the 2-pyridylamino-pyridinium salt **279**, on neutralization with sodium acetate gives a stable free base for which the symmetric structure **280**, or related canonical resonance structures, is proposed (72AJC993).

Rearrangements into a benzothiazole system are recognized in the behavior of some 1,2,4-thiazolidines (**281**), which are produced in the oxidation of thioureas. 5-Arylimino derivatives **281** (R¹ = Ar; R² = Ph; R³ = H) rearrange into corresponding guanidinobenzothiazoles **282** by simple refluxing in ethanol (Scheme 45) (60JCS3240; 84MI2). On the other hand, thiadiazolidines **281** (R¹ = R³ = Me, Et; R² = Ar) are reported to rearrange into the corresponding **282** by treatment with hydrochloric acid in refluxing ethanol (75JA5237; 77AJC1819), some dependence on the nature of substituents being observed in this case (75JA5237).

3. 1,2,3-Thiadiazoles

Rearrangements in this series already have been reviewed in the context of 1,2,3-thiadiazole chemistry (86CHE811). 5-Azidothiadiazoles **284** (R = COOEt, CPh) are unisolable intermediates in the reaction of 5-chloro compounds **283** with sodium azide, since they give a spontaneous rearrangement into diazothiatriazoles **285** (R = COOEt, CPh) (Scheme 46) (82TL1103; 84BSB579; 88BSB163). The reaction depends on the nature of substituent at C(4), strongly favored by electron-withdrawing groups. Compounds **284** (R = Ph; *p*-MeOC₆H₄) show a lower reactivity, whereas the unsubstituted thiadiazole (**284**; R = H) does not rearrange at all (88BSB163). A ring-degenerate rearrangement is also reported (83CC588). In fact, attempts to obtain the 5-diazomethylthiadiazole **286** (R = COOEt) from the tosylhydrazone or the oxime of 5-formyl-4-ethoxycarbonylthiadiazole as precursors, produce directly the rearranged **290** (R = COOEt or COOH) (Scheme 46). Here, the ring-degenerate transformation finds its driving force in the stabilization of the diazo group by the carbonyl function. According to this, the 4-phenylthiadiazole (**286**; R = Ph) does not rearrange (83CC588).

Mechanistically, analogous to what already is suggested for 5-azido- or 5-diazomethyl-1,2,3-triazoles (Section II,C), the participation of open-chain intermediates **287** or **288** is proposed (Scheme 46); the subsequent hetrocyclization engaging the pivotal sulfur and the azido or diazo-methyl side-chain develops into the rearranged **285** or **290**, respectively. On the other hand, a concerted electronic reorganization involving the side-chain



SCHEME 46

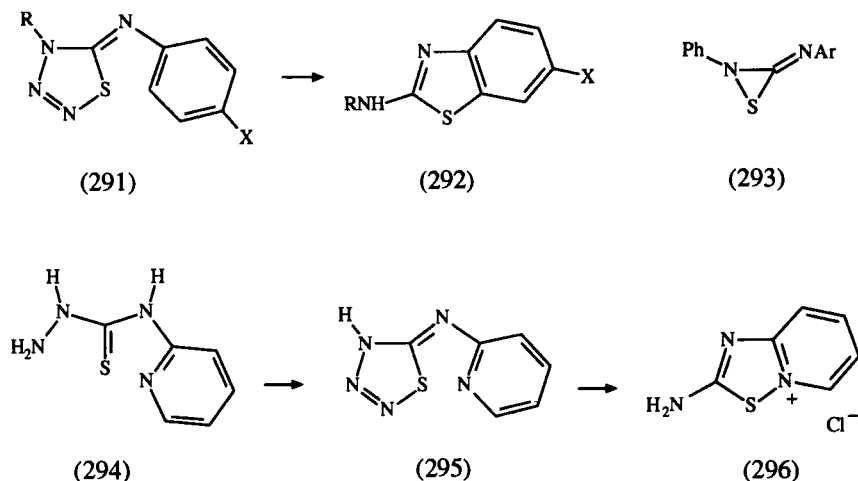
and the thiadiazole ring as in **289** ($X = N$; CH) is also recognized (82TL1103; 83CC588).

4. 1,2,3,4-Thiatriazoles

Rearrangements of 1,2,3,4-thiatriazoles can be systematized in a generalized pattern that proceeds by elimination of nitrogen. In principle, thiatriazole ring opening with consequent extrusion of nitrogen can precede the new ring closure involving the side-chain; however, some concertedness also could result. Examples already have been reviewed in a different context [76AHC145; 82AHC(32)285, 82T3537; 84MI3].

On heating in toluene at 110°C, 5-aryliminothiatriazoles **291** ($R = Me$; $X = H, NO_2$) rearrange into the 2-methylaminobenzothiazoles **292** ($R = Me$) via a displacement at sulfur by the phenyl ring of the arylimino moiety (Scheme 47) (71AP687; 90JHC1993). On the other hand, the 4-phenyl-5-phenyliminothiatriazole (**291**; $R = Ph$; $X = H$) is presumed to be the unisolable precursor of the benzothiazole (**292**; $R = Ph$; $X = H$) in the reaction of the 5-phenylaminothiatriazole with benzyne at 50°C in chloroform. To explain this rearrangement, in addition to the above pathway, a concomitant reaction involving a previous fragmentation of the thiatriazole ring into a thiaziridinimine species (**293**) is also suggested; moreover, heterocyclization on this latter could also involve the phenyl ring originally bound at N(4) of thiatriazole (90JHC923). Isolation of the pyridothiadiazolium salt **296** in the reaction of the pyridylthiosemicarba-

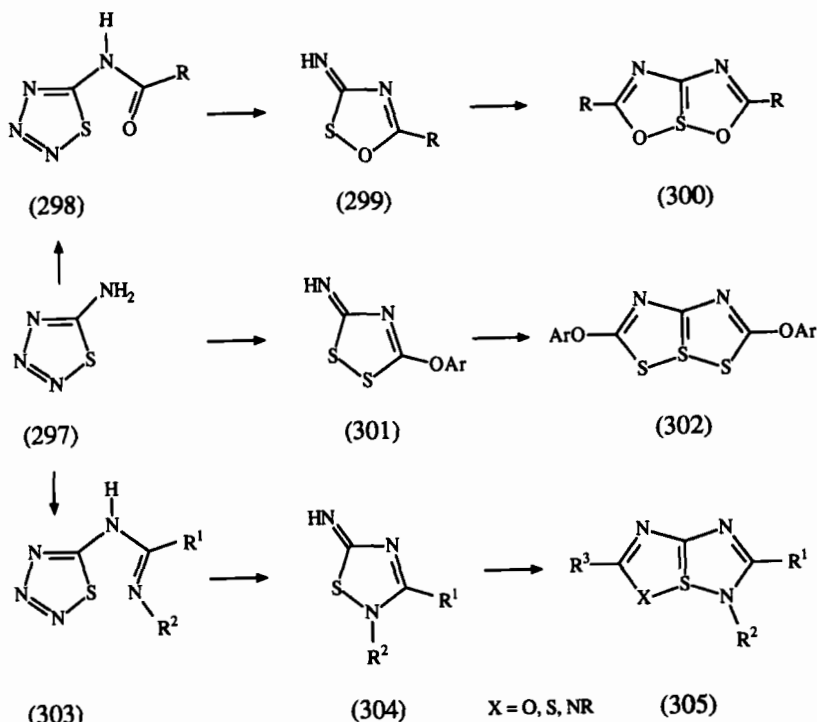
zide **294** with sodium nitrite and hydrochloric acid is explained by a rearrangement of the unisolated, first formed thiatriazole **295** (Scheme 47) (72AJC993).



SCHEME 47

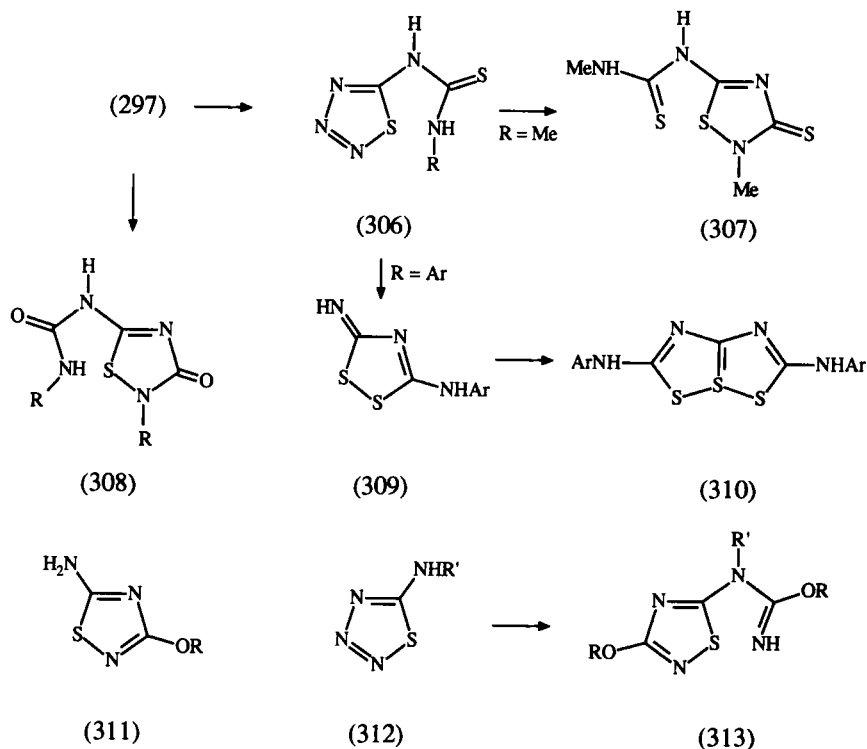
On reacting with acylating reagents, 5-aminothiatriazole **297** gives rise to some rearrangements involving extrusion of nitrogen. The first product, not always isolated, can constitute in turn the substrate for a subsequent reaction (Scheme 48). So, compound **297** reacts with acyl chlorides to give directly 1,6-dioxa-6a-thia-3,4-diazapentalenes **300** through the oxathiazoline **299**, on which a second reagent molecule acts [77AG(E)403, 77CC143; 81BSB89; 82T3537]. By contrast, the reaction of **297** with imidoyl chlorides, gives the isolable iminothiadiazolines **304** as its hydrochloride. From these, a further reaction with imidoyl chlorides, aroyl chlorides, or isothiocyanates produces corresponding azathiapentalenes **305** [77AG(E)403; 79H297; 81BSB89]. For the symmetrically substituted **305** ($R^1 = R^3 = \text{Ph}$; $R^2 = \text{Me}$; $X = \text{NMe}$), X-ray analysis confirms the symmetric structure in the solid state, with a symmetric shape of the N—S—N moiety (84BCJ2581). Regarding rearrangements of the presumed species **298** and **303**, fragmentation may give a key dipolar intermediate on which subsequent heterocyclization can occur. Similarly, the reaction of **297** with thioacylating reagents (aryl chlorothioformates) in acetonitrile gives rearranged dithiazolimines **301** as isolable intermediates. From these, a further thioacylation reaction in the presence of pyridine produces expected trithiadiazapentalenes **302** (Scheme 48) (89M997; 90JPR208).

Significant rearrangements occur on reacting the amino compound **297**



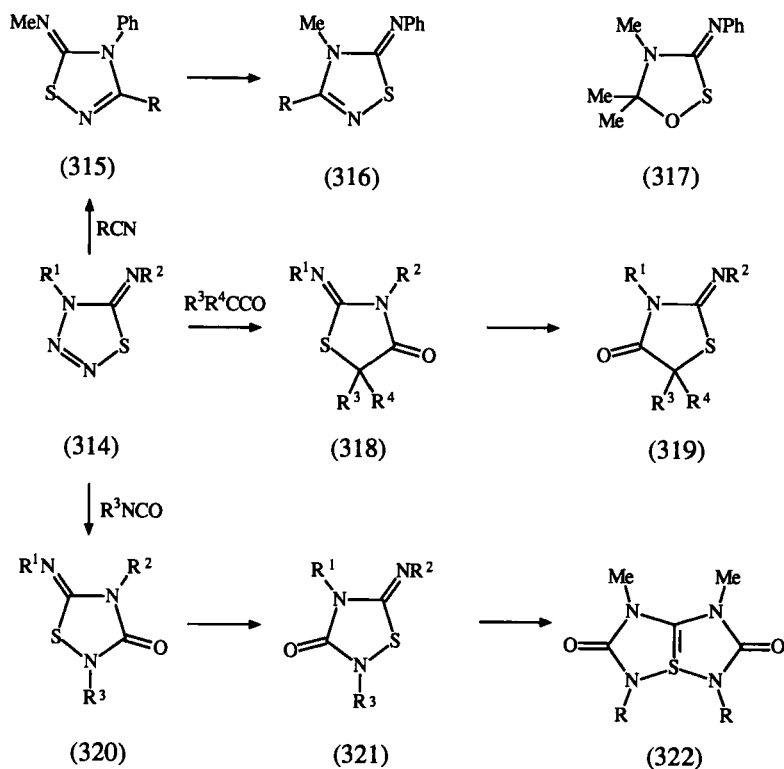
SCHEME 48

with isothiocyanates, isocyanates, cyanates, or electrophilic nitriles. In DMF solvent and in the presence of a tertiary amine catalyst, methylisothiocyanate affords the thiadiazolin-3-thione **307**, whereas aryl isothiocyanates produce trithiadiazapentalenes **310** (Scheme 49) (89JPR115; 90GEP276286). Assuming, at least formally, the formation of a common precursor **306** ($R = \text{Me}, \text{Ar}$), in the case of the methyl compound the involvement of the NCN side-chain gives the thiadiazole-3-thione structure, whereas for the phenyl compound the NCS side-chain first gives the dithiazolimine **309** on which a further reaction with the isothiocyanate takes place. Analogously, the reaction of **297** with two molecules of alkyl or aryl isocyanates produces the 5-ureidothiadiazolin-3-ones **308** (Scheme 49) (88ZC327; 91GEP281188). *N*-monosubstituted aminothiatriazoles **312** and isothiocyanates produce thiadiazole-3-thiones, too (89JPR115); however, the results can be rationalized by a preliminary addition of the $\text{C}=\text{N}$ dipolarophile of the reagent to the $\text{S}(1)\text{—N}(4)$ moiety of the thiatriazole ring. Similar results are observed in a reaction with isocyanates



SCHEME 49

(79JOC3840; 87JPR409). The amino compound **297** reacts with alkyl and aryl cyanates in aprotic solvent to give 5-aminothiadiazoles **311** ($R = \text{alkyl, aryl}$), presumably via rearranging species such as **303** ($R^2 = \text{H}; R^1 = \text{OR, OAr}$); trichloroacetonitrile reacts similarly (85JOC1295). Monosubstituted aminothiatriazoles **312** react with two molecules of cyanates leading directly to thiadiazoles **313**; on this basis, a cycloaddition of the first cyanate molecule to the $S(1)-N(4)$ group of the ring is proposed as a key step in these reactions, which proceed bimolecularly (85JOC1295). This explanation can be questioned, however, taking into account mechanistic observations on the reaction of thiatriazolines with heterocumulenes (where two consecutive cycloaddition-elimination processes are proposed, see below). In this context, a reinvestigation of these reactions is appropriate. Formation of 2-amino-5-methyl-1,3,4-oxadiazole in the thermolysis (40°C) of the *N*-acetylhydrazinothiatriazole (85ZC136) can be explained by assuming extrusion of sulfur from a first-formed ring-fragmentative intermediate, followed by subsequent ring closure involving the acetylhydrazino moiety.



SCHEME 50

Rearrangements occur in the reaction of 5-iminothiatriazoles **314** with electrophilic nitriles and heterocumulenes (Scheme 50). An initial cycloaddition of the unsaturated reagent to the iminothiatriazole moiety acting as a masked 1-3 dipole explains these reactions. The other possible mechanism proceeding by a cycloaddition at positions S(1)—N(4) of the triatriazole ring is discarded on the basis of experimental evidence and mechanistic investigations. On the other hand, in these reactions the rearrangement product arising from the first cycloaddition–elimination pathway constitutes in turn the substrate for a subsequent reaction with the same unsaturated reagent.

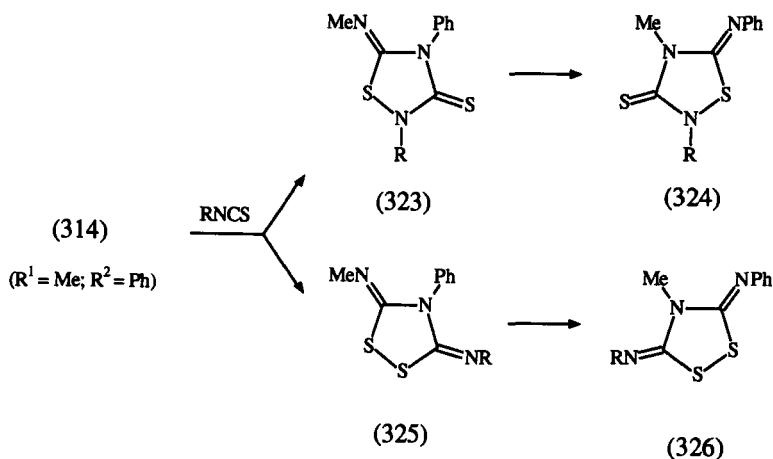
The phenyliminothiatriazole **314** ($R^1 = \text{Me}$, $R^2 = \text{Ph}$) reacts with ethyl cyanoformate or *p*-toluensulfonyl cyanide to afford directly the phenyliminothiadiazolines **316** ($R = \text{COOEt}$, *p*- $\text{MeC}_6\text{H}_4\text{SO}_2$) as a result of two consecutive reactions going through methylimino isomers **315** (91JHC333). In acetone solvent, the intermediate formation of the oxathiazolidine **317**

on which the unsaturated reagent acts more easily is suggested. However, the existence of **317** arising from two consecutive processes of cycloaddition-elimination involving the carbonyl of the reagent is supported by the thermolysis of compound **314** ($R^1 = \text{Me}$; $R^2 = \text{Ph}$) in acetone (90JHC1993). On reacting with ketenes, iminothiatriazoles **314** give **318** and/or **319** [78JCS(P1)1440, 78JOC4951; 91BSB29]. In the case of the reaction of diphenylketene on **314** ($R^1 = \text{Et}$; $R^2 = \text{Me}$), previously assigned structures **318** and **319** [78JCS(P1)1440] may be inverted (91BSB29). In the reaction of **314** ($R^1 = \text{Me}$, $R^2 = \text{Ph}$) with bis-ethoxycarbonylketene ($R^3 = R^4 = \text{COOEt}$) at 0°C , the corresponding first reaction product **318** can be isolated. From this, by a further reaction with the same reagent, the end product **319** arises (91BSB29).

The reaction of iminothiatriazoles **314** with isocyanates directly afford thermodynamically favored thiadiazolidines **321** (Scheme 50) [76AG(E)489; 90JHC1059], the formation of which is explained by two consecutive cycloaddition-elimination processes going through **320** (91BSB27, 91JHC405). This interpretation is also enhanced by the observation that in some cases the first reaction product can be isolated as such, and gives the thermodynamically favored thiadiazolidine when treated with an excess of the isocyanate (91BSB27, 91JHC405). As regards the isomerization reaction, the intermediacy of a tetraazathiapentalene-2,5-dione structure is suggested and supported by the reaction of thiadiazolidines **320** ($R^1 = R^2 = \text{Me}$) (or, the same, **321** when $R^1 = R^2 = \text{Me}$) with isocyanates (RNCO) and the isolation of corresponding tetraazathiapentalenes **322** (91JHC405).

The rearrangements, which 4-methyl-5-phenyliminothiatriazole (**314**; $R^1 = \text{Me}$, $R^2 = \text{Ph}$) gives rise to on reacting with an excess of isothiocyanates, have been extensively explored (77JOC1159; 78JOC4951; 82T3537). Kinetic investigations and cross-over experiments utilizing various isothiocyanates having different electrophilicity supported the results. Thus, an initial cycloaddition-elimination reaction could engage on the one hand the 1,3-dipole of the phenyliminothiatriazole and on the other the $\text{C}=\text{N}$ and/or $\text{C}=\text{S}$ moiety of the isothiocyanate, leading to thiadiazolidines **323** and/or dithiazolidines **325**, respectively (Scheme 51). This reaction could be followed by a series of cycloaddition-elimination processes involving the same reagent, and proceeding via tetraazathiapentalene- or diazatrithiapentalene-type intermediates, up to the end products such as **324** and/or **326**. For this reaction, which we consider beyond the scope of the present treatment, we refer to the original papers (88JHC1459; 89BSB879; 90BSB391, 90JHC199, 90T1281).

The 4-substituted-5-sulfonylimino-1,2,3,4-thiatriazoles also rearrange on reaction with unsaturated reagents [75JOC1728; 80AG(E)276; 82T3537;



SCHEME 51

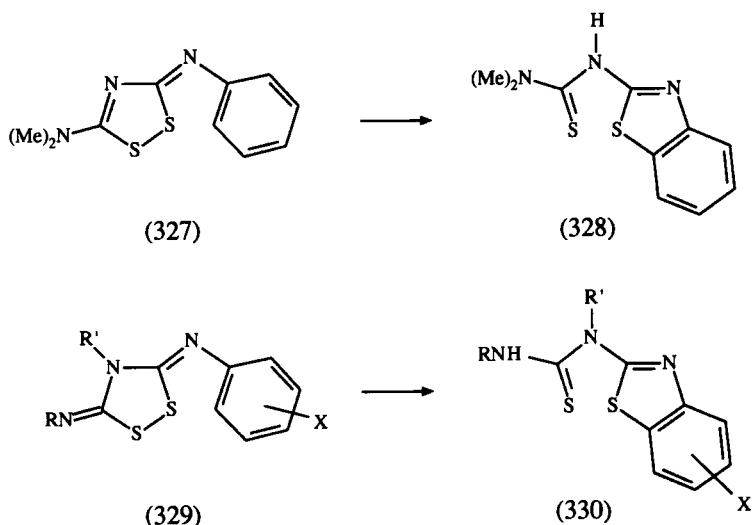
87MI1; 90JHC2133]. Here, the reactions are explained by assuming preliminary fragmentation into a thiaziridinimine intermediate. On this species, or on its dipolar opened form, the cycloaddition reaction can take place. On the other hand, the participation of the sulfonylimino side group in the extrusion of nitrogen is also suggested (90JHC2133).

B. REARRANGEMENTS INVOLVING CLEAVAGE OF AN S—S BOND

1. 1,2,4-Dithiazoles

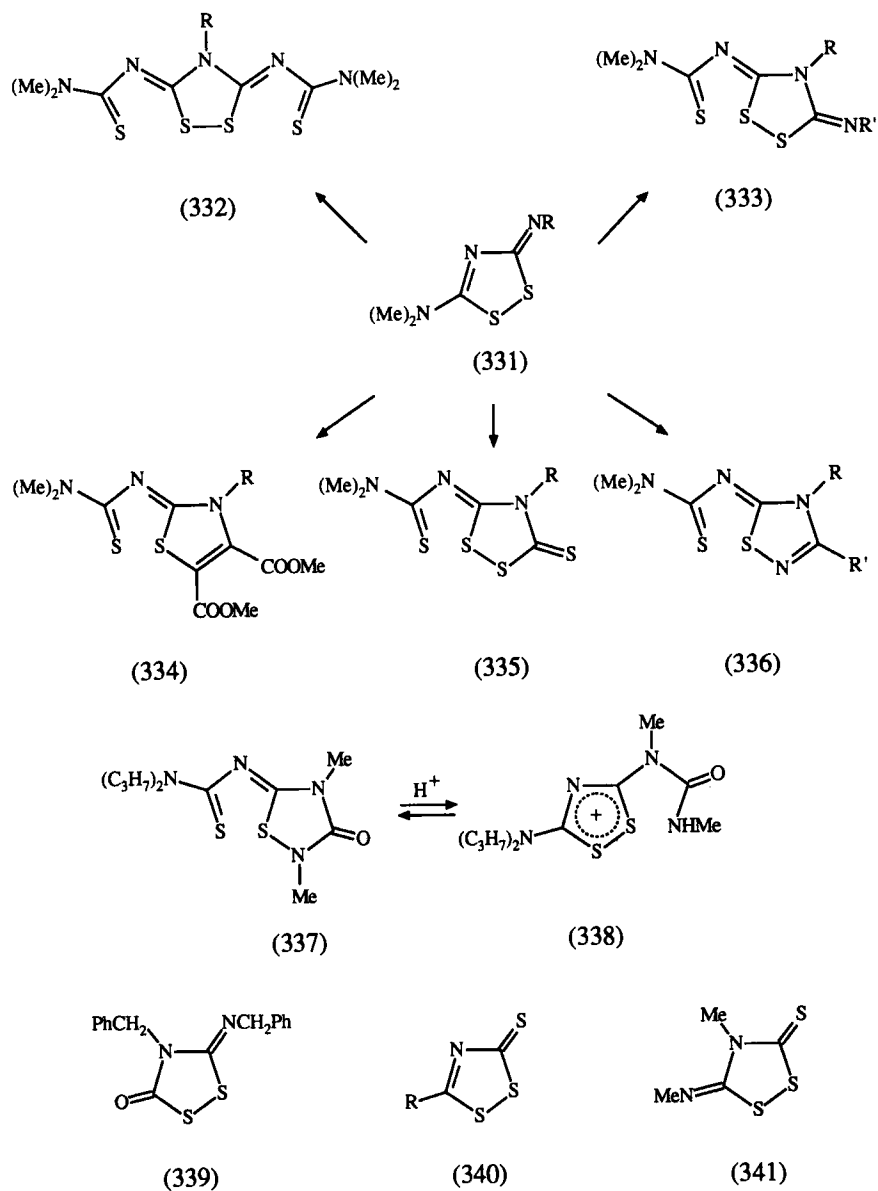
On reflux in toluene, the 3-phenylimino-dithiazole **327** rearranges into the benzothiazole **328** (Scheme 52) (74JOC2233), according to the well-known displacement at sulfur by a phenyl ring of a side-chain. It seems noteworthy that in the O—N-bond-containing substrates, similar rearrangements presuming a reaction at the pivotal nitrogen do not occur (81AHC141). In the presence of mineral acids, dithiazolidines **329** analogously rearrange into benzothiazoles **330** (Scheme 52) (82AJC405); here, the reaction takes place from a protonated substrate and depends to some extent on the nature of substituents in the dithiazolidine ring.

Rearrangements proceeding via cycloaddition of an unsaturated reagent with consequent cleavage of the S—S bond are representatively shown in Scheme 53. Imino compounds **331** react with dimethylthiocarbamoyl isothiocyanate to give **332** (72CB1568; 74JOC2228), for which X-ray analysis indicates some interactions among the four sulfur atoms in a collinear



SCHEME 52

position (72CC1153; 73JA6073). Similarly, the reaction of **331** and isothiocyanates, dimethyl acetylenedicarboxylate, carbon disulfide, or nitriles produces compounds **333**, **334**, **335**, and **336**, respectively (74JOC2225, 74JOC2228). Other reactions of iminodithiazoles with acetylenedicarboxylates (67BSF2865; 69CJC2039; 70MI2), or with carbon disulfide, carbonyl sulfide, carbon dioxide, and isocyanates (77CB285), give the corresponding cycloaddition-rearrangement compounds. Interestingly, the NMR spectrum (in trifluoroacetic acid) of compound **337**, arising from the 3-methylimino-5-(diisopropylamino)dithiazole and methyl isocyanate suggests the presence of dithiazolium species **338**, according to an equilibrium which depends on pH (77CB285). Cycloaddition-rearrangement processes also take place in the reaction of 3-iminodithiazolines with activated alkenes (75TL3387) or sulfonyl chlorides (77TL1729). Similar reactions, via thiapentalene-like intermediates of course, are also reported for the 3-benzyliminodithiazolidin-5-one **339** and heterocumulenes (isocyanates, isothiocyanates, or ketenes), carbonyl sulfide being the extruded species in this case (90JHC1629). The 1,2,4-dithiazol-3-thiones **340** behave similarly in the reaction with activated alkynes (67BSF2865; 69CJC2039; 74JOC2228; 84MI4), benzyne (76BSF120), or dialkylcyanamides (89CL1357). In the case of the dithiazolidine **341**, where two 1,3-dipolar sites can be recognized, the reaction with electrophilic nitriles engages the S—C=S moiety. Thus, two consecutive cycloaddition-elimination reactions involving thiapentalene-like intermediates produce thiadiazolin-



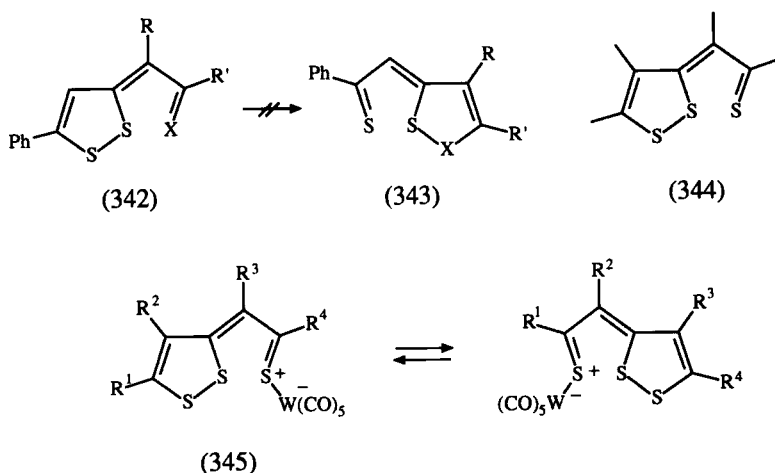
SCHEME 53

5-thiones **273** as final products, methyl isothiocyanate being the extruded species (91JOC3268).

2. 1,2-Dithioles

Theoretical calculations and spectroscopic evidence had suggested the photoinduced rearrangement of 1,2-dithioles **342** ($X = O$; NPh) into isomers **343**, and the reverse process in a thermally induced reaction (72JA651). A subsequent, more careful, study has however confirmed that irradiation of **342** produces a simple geometrical isomerization around the carbon—carbon double bond [73CC123, 73HCA597, 73JCS(P1)2837; 74AG(E)349; 77ACS(B)683].

For the generalized dithioles **344**, some consideration on the question of whether they represent valence isomers or resonance forms of a symmetrical trithiapentalene species is reported (71AHC161; 84MI5). A degenerate rearrangement is claimed in the pentacarbonyltungsten(0) complex **345**, for which crystallographic investigations (X-ray, S—S bond length) suggest the dithiole rather than the trithiapentalene structure (83CC289). The fluxional behavior of this complex, pointed out by dynamic ^1H -NMR in the symmetrically substituted substrates, is ascribed to an intramolecular equilibrium (Scheme 54). In the case of **345a**, spectral data and the



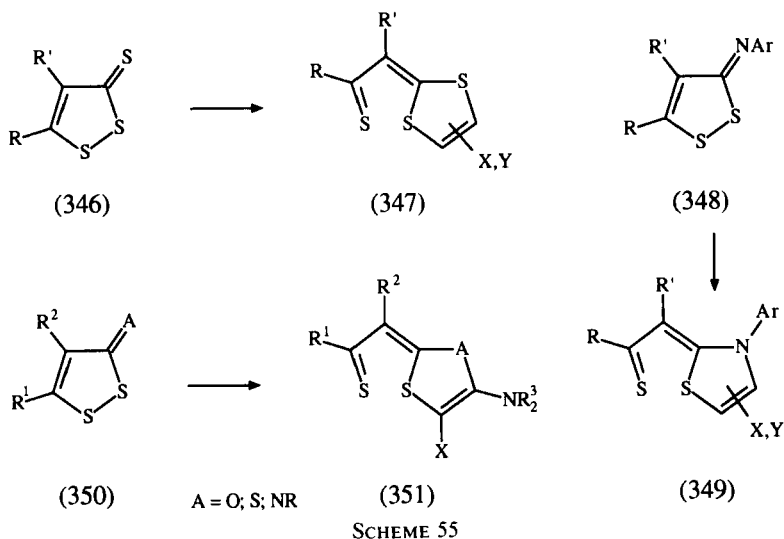
a: $R^1 = R^4 = \text{H}$; $R^2 - R^3 = (\text{CH}_2)_3$

b: $R^1 = R^4 = \text{Me}$; $R^2 = R^3 = \text{H}$

SCHEME 54

coalescence temperature allow the calculation of a free energy of activation, ΔG^\ddagger , of 14.7 kcal mol⁻¹.

As expected, the dithiol-3-thiones **346** react with activated alkynes following the cycloaddition-rearrangement pathway **346** \rightarrow **347**. The reaction involves the S—C=S dipolar group, with consequent cleavage of the ring S—S bond (Scheme 55); benzyne and ketenes behave similarly. 3-Arylimino compounds **348** react with activated alkynes to give **349**, and generalized 1,2-dithioles **350** (A = O; S; NR) react with ynamines (XC \equiv CNR₂) to rearrange into the corresponding oxathioles, 1,3-dithioles and thiazoles **351** (Scheme 55) [69CJC2039; 72JCS(P1)41; 73BSF270; 76BSF115, 76BSF120]. Some of these reactions already have been reviewed [82AHC(31)63; 84MI6].



IV. Rearrangements Involving the Pivotal Carbon Atom in the Starting Ring

In this section we consider rearrangements involving an annular carbon as the pivotal center. This structural pattern affects either reactivity or reaction mechanism. In fact, there are some relevant differences in energy requirements for these rearrangements in which bond fission involves not a nitrogen or sulfur atom but a carbon atom. Detailed mechanistic studies so far are lacking; however, the carbon atom as a pivotal center might render the concerted ring closing-ring opening process unfavorable

[76JCS(P1)315]. On the other hand, acid catalysis, which enhances electrophilicity of the pivotal carbon, is generally observed.

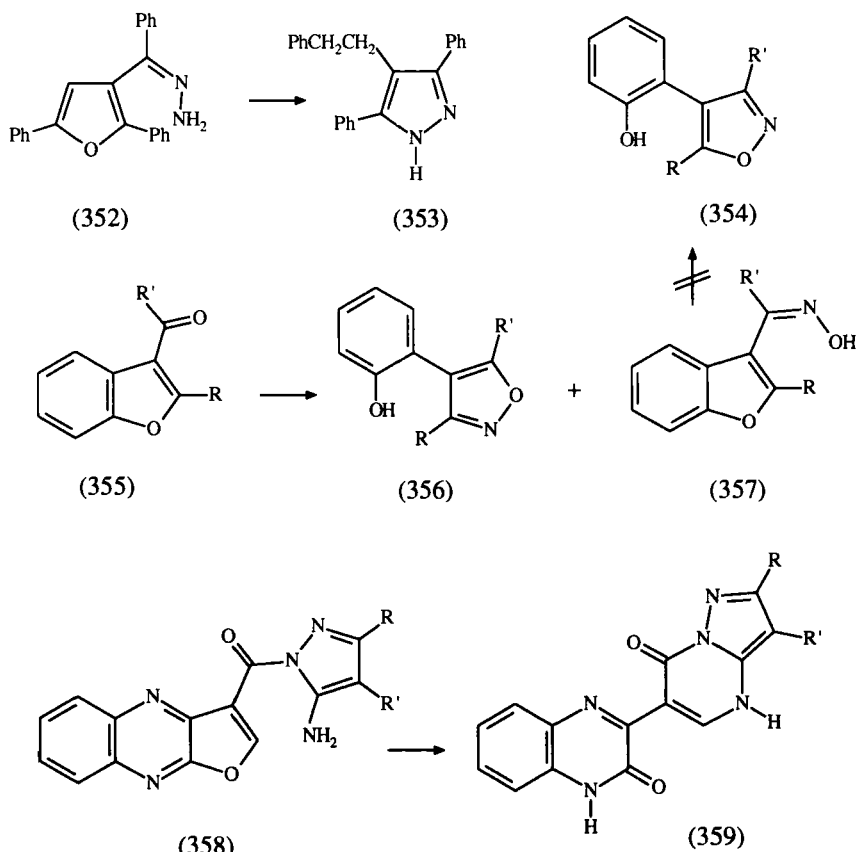
Topics will be presented according to the number of heteroatoms in the starting heterocycle. The reacting side-chain can be saturated or unsaturated, and can be conjugated or nonconjugated with the rearranging ring. Rearrangements proceeding by nucleophilic attack at the same carbon carrying the side chain (*ipso*-attack) and involving spiro compounds as intermediates will also be considered.

REARRANGEMENTS

1. Five-Membered Heterocycles Containing One Heteroatom

A typical rearrangement can be recognized in the Wolff–Kishner reduction of the 2,5-diphenyl-3-benzoylfuran (73MI1). In addition to the expected reduction product, the reaction gives the pyrazole **353**, the formation of which is explained through the hydrazone **352** (Scheme 56), although hydrazinolysis of the furan ring is not excluded (56JOC297). The acylbenzofurans **355** react with hydroxylamine to produce mixtures of isoxazoles **356** and oximes **357** in variable ratios, depending on the nature of R and R' and on the experimental conditions. The isolated oximes, however, do not rearrange into the corresponding isoxazoles **354** (Scheme 56). The direct formation of isoxazole isomers **356** is explained by a nucleophilic attack of the reagent at the C(2) of the acylbenzofuran, for which crypto- β -diketone character is claimed (63BSF1746). To this reactivity, which differs from our general pattern, rearrangements of 3-acylbenzofurans **355** into pyrazoles or pyrimidines by reaction with hydrazine or guanidines, thioureas, ureas, and amidines can be related (66BSF1587; 67BSF356; 70MI3; 74HC95; 77BSF369). A real rearrangement involving a four-atoms side-chain in a condensed furan series is suggested to occur from **358** into **359** (Scheme 56). Here, structures **358** represent unisolated intermediates in the reactions of 3-(*N,N*-dimethylcarbamoyl)furo-[2,3-*b*]quinoxaline hydrochloride with some 5-amino-1*H*-pyrazoles (89JHC1159).

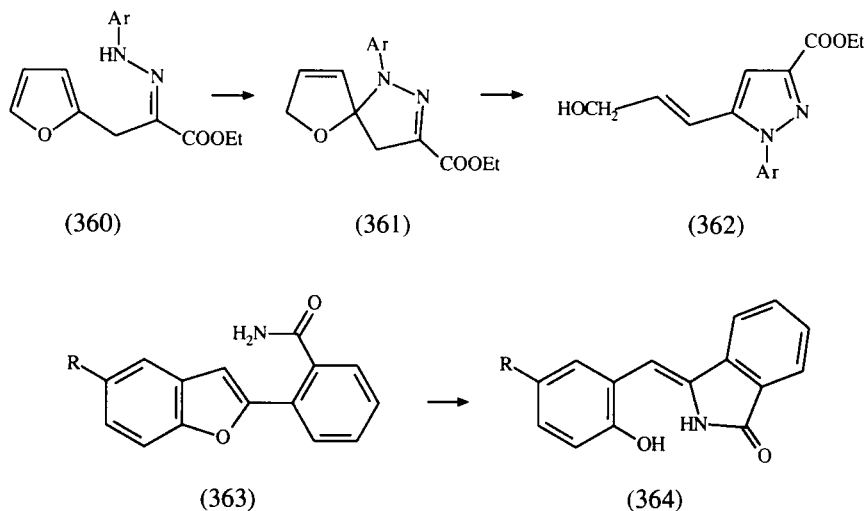
On reacting with sulfuric acid, arylhydrazones **360** rearrange into pyrazoles **362**. An *ipso*-attack of the arylhydrazone nitrogen atom at the C(2) of the protonated ring, followed by an acid-catalyzed ring-opening of the spiro compound **361** (Scheme 57) explains the reaction [79CC221; 82IJC(B)638]. In the same way, the base-promoted rearrangement of amides **363** into **364** proceeds via *ipso*-attack by the amide anion, followed by ring opening of the benzofuran moiety (90JHC605).



SCHEME 56

In the pyrrole or indole series, some typical rearrangements that have been known for many years are found in the reaction of 3-acylpyrroles or 3-acylindoles with hydrazine (73M11). The final compounds, among which the corresponding Wolff-Kishner reduction products are not always found, are pyrazoles **366** and **368**, respectively. Although suitable mechanistic studies on this topic are not reported, the rearrangement assumes hydrazones **365** and **367** as intermediates (Scheme 58) and nucleophilic attack at the C(2) site of the ring by the hydrazone group (73M11).

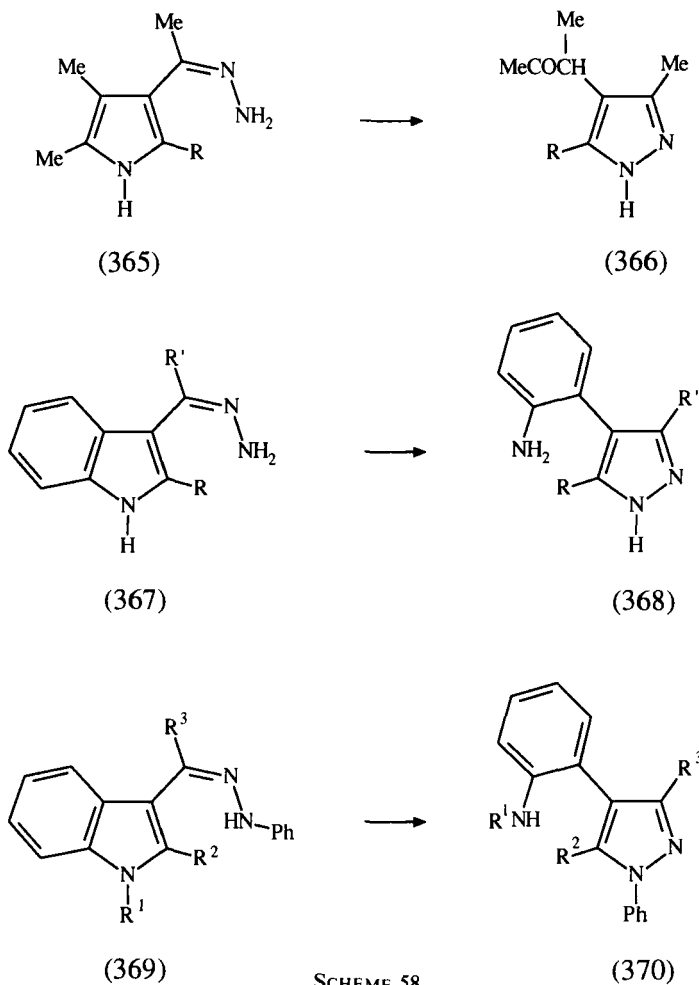
The intermediacy of phenylhydrazones **369** ($R^1 = H$; $R^3 = Me$) is suggested in the transformation of some 2-alkylindoles into the corresponding pyrazoles **370** by the reaction with phenylhydrazine hydrochloride in refluxing acetic-hydrochloric acid (Scheme 58) (76CJC1020). Here, after preliminary acetylation at C(3) of the indole by the acetic-hydrochloric



SCHEME 57

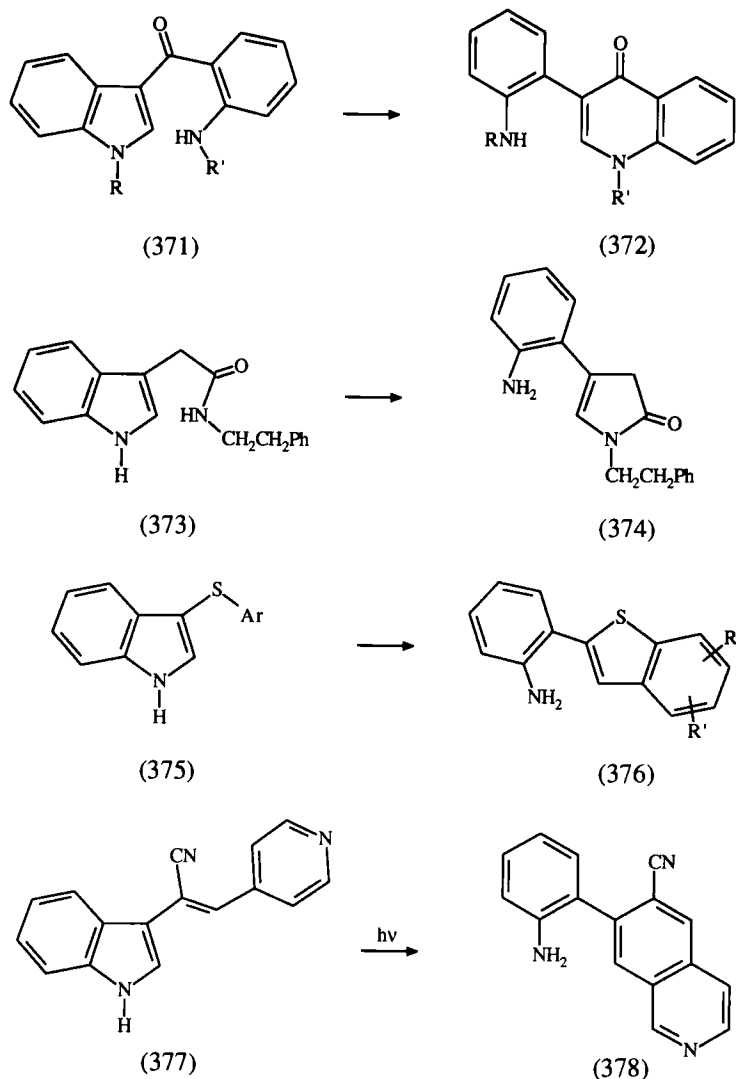
acid mixture follows formation of phenylhydrazones and subsequent acid-catalyzed rearrangement. In support of this, 3-acetyl-2-methylindole under similar conditions yields pyrazole **370** ($R^1 = H$; $R^2 = R^3 = Me$). Bulky substituents at C(2) preclude the rearrangement, since the reaction goes through an acid-catalyzed addition of phenylhydrazine to the indole (76CJC1020). Several phenylhydrazones **369** undergo the acid-catalyzed rearrangement into the corresponding pyrazoles **370** (77JHC1183; 86H3181). In some cases, e.g., **370** ($R^1 = H, Me$; $R^3 = COOEt$; or, $R^1 = H$; $R^3 = COMe$), the rearranged pyrazoles are unisolable intermediates since they suffer subsequent reaction between the amino group and substituent R^3 (86H3181). As expected, the rearrangement can be rationalized by a 6π -electron heterocyclization involving protonated species, with subsequent breaking of the N—C bond of the ring favored by the acid catalysis. This typical reactivity can be also recognized in the acid-induced ring opening into pyrazoles of some cycloadducts arising from pyrroles or indoles and nitrilimines (72TL4703; 77JHC1183; 78JHC293, 78JHC1485). Furthermore, opening of the indole ring at the N—C(2) bond level in a cycloaddition-rearrangement pattern also occurs in the reaction of indoles with acetylenic esters [72JCS(P)1569; 73CPB2770].

Acylindoles **371**, where a four-atoms side-chain can be recognized, give rise to an acid-catalyzed rearrangement into **372** (Scheme 59) (69JOC2868). Analogously, by heating with polyphosphoric acid, compound **373** first rearranges into **374**, which in turn gives reactions involving the functional groups (56CB2498; 67CB1546). Interestingly, the 3-(arylthio)indoles **375**



containing electron-rich aryl groups react with polyphosphoric acid to rearrange into 2-(2-aminophenyl)benzothiophenes **376** (Scheme 59); by contrast, in the absence of electron-rich aryl groups (e.g., Ar = Ph), the reaction gives only the isomerization to 2-(aryltio)indoles. The rearrangement is explained by a cyclic intermediate involving the C(2) of the heteroring and the electron-rich aryl moiety, and is considered to depend on the stabilization of positively charged intermediates and on the use of polyphosphoric acid. In fact, trifluoroacetic acid caused the isomerization of **375** into the 2-(aryltio) derivatives (90CC1072).

Irradiation of **377** gives directly **378** (Scheme 59). Here, heterocyclization at C(2) by the side-chain in the correct configuration, followed by the

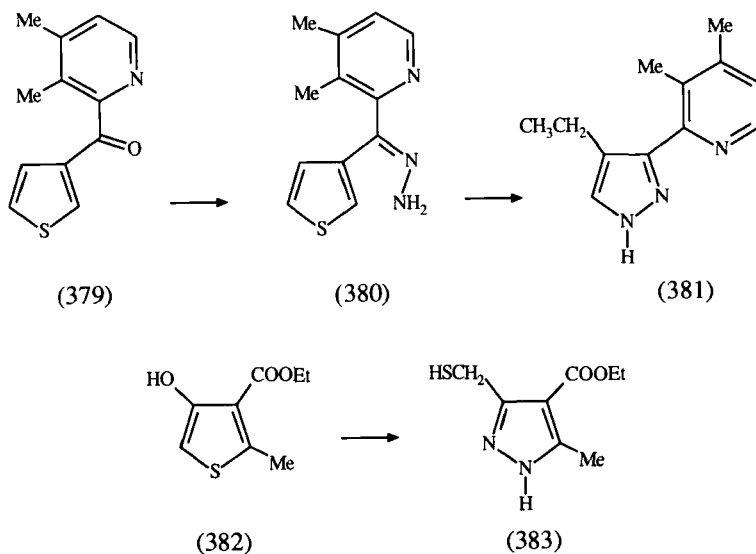


SCHEME 59

expected ring opening of the indole in a cyclic intermediate, leads to the final product. However, irradiation of **377** in the presence of an oxidant causes aromatization of the cyclic intermediate without any rearrangement (75TL4567).

In the thiophene series a Wolff-Kishner reaction on the 3-aryl compound **379**, in addition to the expected reduction product, affords the pyrazole **381**. A typical rearrangement of the hydrazone **380**, followed

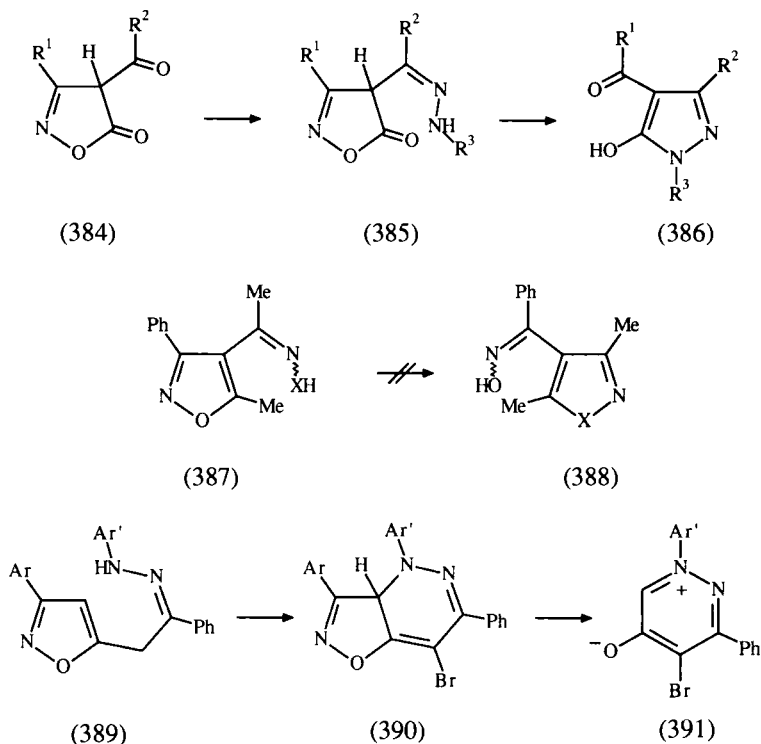
by reduction of the resulting side-chain, explains the result (Scheme 60) (78JHC193). A similar reaction is documented for 3-benzoylbenzothiophene (55G245). On the other hand, the ethoxycarbonylthiophene **382** reacts with hydrazine to give the ethoxycarbonylpyrazole **383** (71CHE707), which can be rationalized through hydrazinolysis of the thiophene ring.



SCHEME 60

2. Five-Membered Heterocycles Containing Two Heteroatoms

a. *Isoxazoles–Oxazoles.* The 4-acyl- Δ^2 -isoxazolin-5-ones (**384**) react with hydrazine or phenylhydrazine to give 5-hydroxypyrazoles (**386**) directly. The reaction presumes the preliminary formation of hydrazones or phenylhydrazones (**385**), which will rearrange through nucleophilic attack by the side-chain at C(5) of the isoxazole and the consequent fission of the O—C(5) bond (Scheme 61). Hydrolysis of the resulting oxime under reaction conditions will then give the final products (71S216). This pattern could also include the rearrangement of the diazoamino compound derived from the diazotization of the 4-amino-3,5-dimethylisoxazole into the 1-(3,5-dimethylisoxazole-4-yl)-4-acetyl-5-methyl-1,2,3-triazole (62JCS2083). By contrast, attempts to realize a photoinduced rearrangement of **387** (X = O, NHP) into **388**, hypothesized on the basis

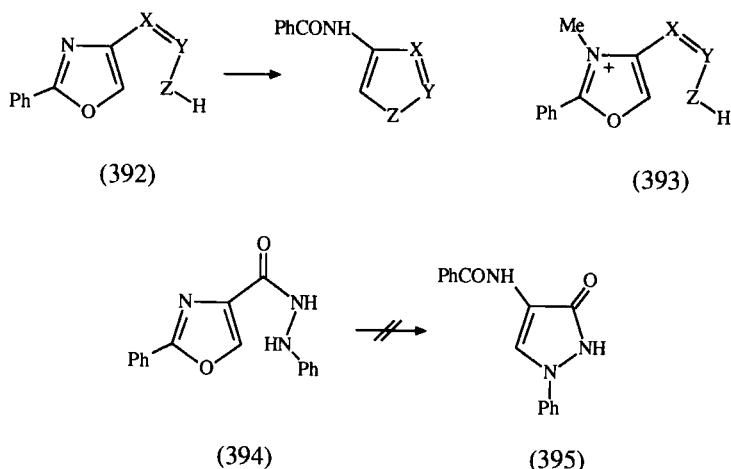


SCHEME 61

of an initial heterocyclization of the side group at C(5) of the isoxazole ring, were unsuccessful (75JA6484).

Rearrangement of arylhydrazones of 5-phenacylisoxazoles **389** into the 5-oxidopyridazinium betaines **391** (Scheme 61) does not fit the general model. According to the proposed mechanism, by first reacting with bromine in chloroform the arylhydrazone moiety then would react electrophilically with the C(4) position of the isoxazole ring. The fragmentative reorganization of **390** involves the isoxazole moiety and elimination of the ArCN species (83TL1285).

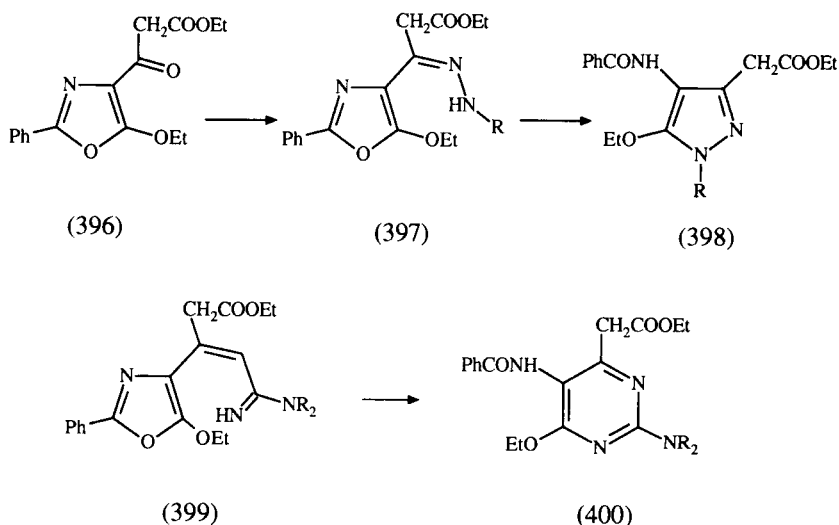
Rearrangements of oxazoles **392** and **393** (Scheme 62), which assume nucleophilic attack of the side-chain at the C(5) position and consequent fission of the ring $\text{O}-\text{C}(5)$ bond, have been considered [76JCS(P1)315]. Nevertheless, the phenylhydrazide **394** does not rearrange into the expected **395** and remains unchanged under various conditions. In this context, unsuccessful attempts are reported for some structurally related 4-substituted oxazoles, whereas specific examples concerning oxazolium substrates **393** are not mentioned [76JCS(P1)315].



SCHEME 62

Examples belonging to this pattern come from the reaction of oxazole-ketoester **396** with hydrazine or methylhydrazine. Here, the reaction produces directly benzoylaminopyrazoles **398** through unisolated hydrazones **397** (Scheme 63) (84H2463). As a possible generalization of this rearrangement, 4-ketooxazoles can be considered as precursors of 4-aminopyrazoles (exploiting the reaction with hydrazines), and of other amino heterocycles (exploiting the reaction with various bidentate nucleophiles). Thus, compounds **396** react with guanidine or *N,N*-dimethylguanidine to give rearranged pyrimidines **400** via unisolated **399** (Scheme 63) (84H2463).

The 4-iminooxazole **401** and electrophilic heterocumulenes $R-N=C=Y$ in refluxing benzene furnishes directly compounds **403** and/or **404**, via a rearrangement of the dipolar intermediates **402** (Scheme 64). In this reaction, an attack at the C(5) site of the oxazole by the N or Y nucleophile is demanded; the driving force could stay in the good leaving group acting in the rearranging ring (85CC1614). With isocyanates ($Y = O$), the heterocyclization engages the oxygen atom to yield **404** as the kinetic product; in some instances, the first formed product goes to **403**, which then represents the predominant component at the end of the reaction. On reacting with isothiocyanates ($Y = S$), the heterocyclization involves the nitrogen atom, by which compounds **403** ($Y = S$) form (85CC1614). Heterocumulenes with a lower electrophilicity do not react. The reactions of **405** with isocyanates, isothiocyanates, and ketenes can be related to this reactivity (79JOC3991). In a similar manner, the reaction of 4-acetyloxazole **406** with malononitrile in the presence of sodium hy-

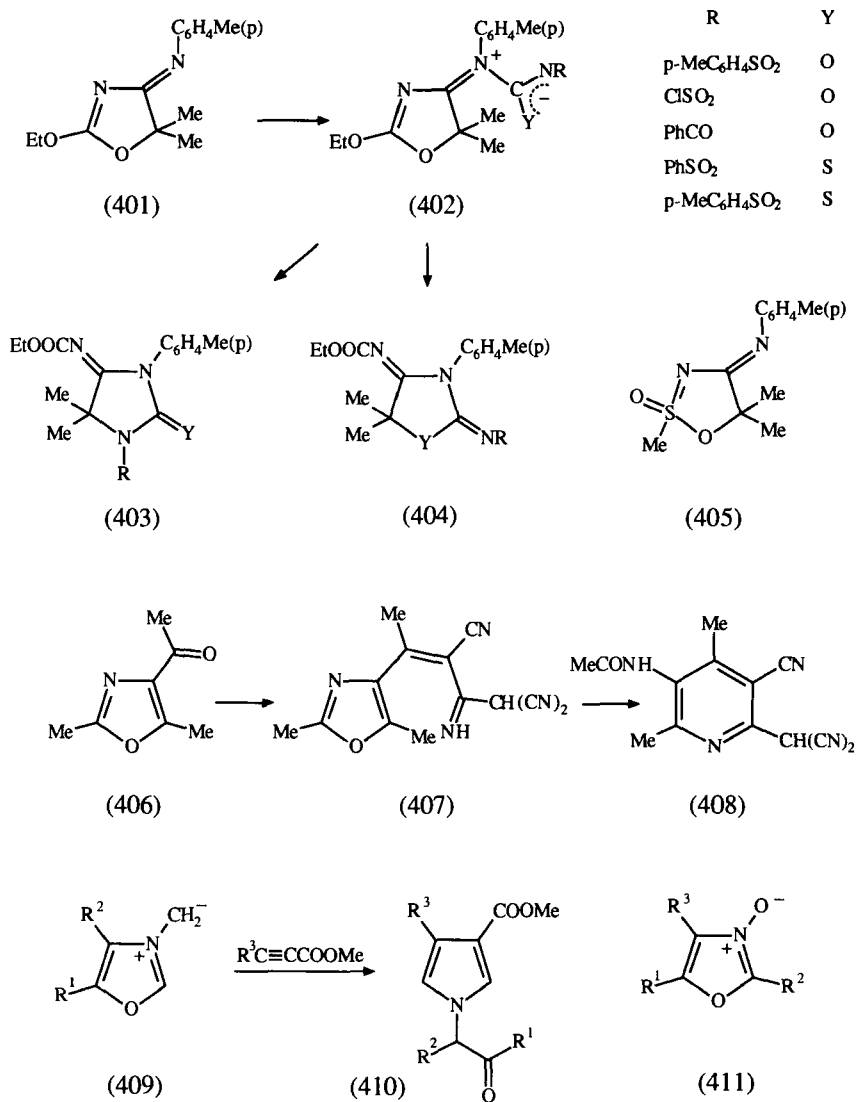


SCHEME 63

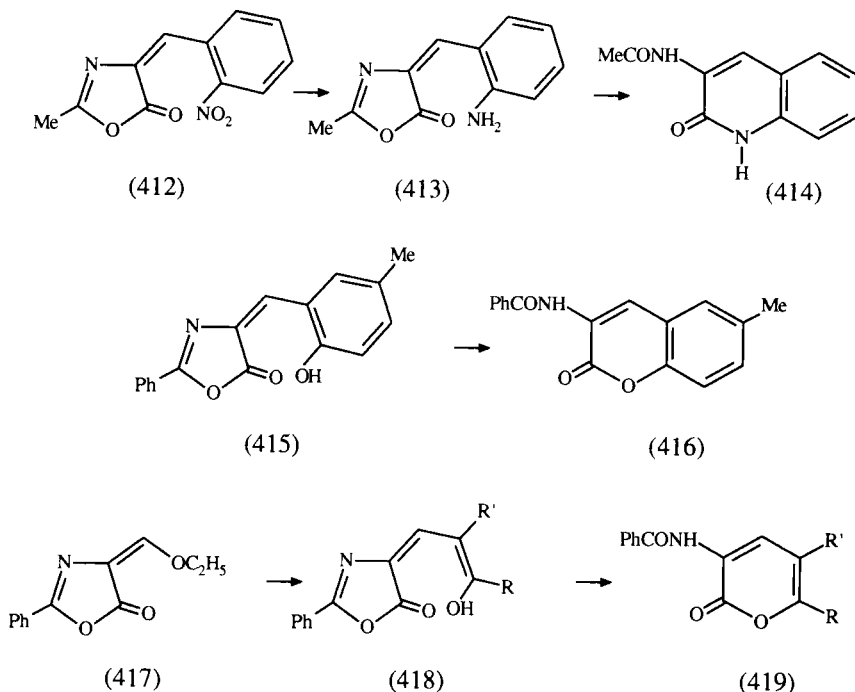
dioxide gives the acetylaminopyrimidine **408** through rearrangement of the presumed **407**, involving the participation of a four-atoms side-chain (Scheme 64) (72JOC1047).

A comparable rearrangement comes from the reaction of the elusive oxazolium-azomethine-ylide **409** with acetylenic esters: first cycloaddition engages the electrophilic C(2); this then is followed by ring opening of the oxazole moiety to give pyrroles **410** (85CC1108). A similar process is observed for thiazolium and benzothiazolium azomethine-ylides (85CC1108) and thiazolium-ylides (76JOC187) in which a C—S bond is cleaved. In this context, ring opening of the thiazole heterocycle in a cycloaddition-rearrangement pattern occurs in some reactions of thiazoles with acetylenic esters [75CC155; 76CHE837, 76JCS(P1)1269]. Rearrangements via a bicyclic intermediate involving a side-chain and the C(2) of the oxazole ring also take place in reactions of the *N*-oxides **411** with aryl isocyanates (70CPB2000; 78CPB3798).

Reduction of nitrobenzylideneoxazolone **412** having the *E* configuration gives directly the acetylaminquinolinone **414**, resulting from the rearrangement of the unisolated *E* amino compound **413E** (Scheme 65). The importance of the correct configuration is well supported, since the reduction of the *Z* nitrobenzylideneoxazolone isomer gives the unrearranged amino compound (**413Z**) (85CHE514). This rearrangement parallels the formation of benzolaminocumarine **416** from **415**, or the generalized pattern **418** → **419**, which is recognizable in the reaction of



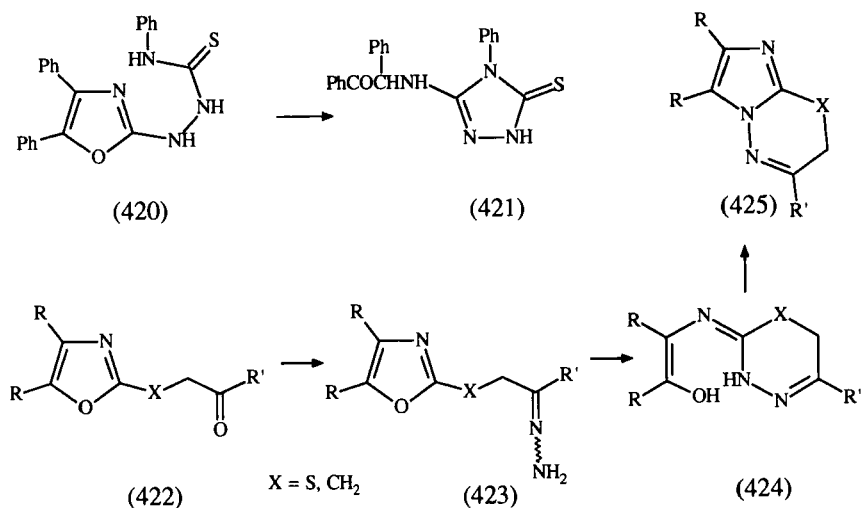
SCHEME 64



SCHEME 65

4-ethoxymethyleneoxazolone (**417**) with active methylene compounds (Scheme 65) (63CB1428; 73M11). [For a criticism on structural aspects of these rearranging substrates, see 90JCS(P1)1459; 91JCS(P1)2183]. The rearrangement of **415** into **416** also takes place by irradiation of **415**, an enhanced nucleophilicity of the hydroxy group in the excited species being suggested (66JHC235). A related transformation also can be assumed in obtaining **419** ($R = \text{Ph}$; $R' = \text{H}$) from the reaction of 2-phenyl-5-oxazolone with benzoylacetylene in acetic anhydride (68CPB1576).

Some rearrangements in the oxazole and benzoxazole series are explained via an *ipso*-attack of the side-chain at the C(2) site of the ring, with subsequent (or concerted) breaking of the O—C(2) bond. In this case the reacting heterocycle participates with a single atom in the formation of the final ring. See, for example, the thermal rearrangement of **420** into **421** (65JPR280), or the formation of compounds **425** in the reaction of oxazoles **422** ($X = \text{S}, \text{CH}_2$) with an excess of hydrazine in acetic acid on heating (Scheme 66) [82H2119; 83JCS(P1)3027]. In this last reaction, the rearrangement assumes the preliminary formation of hydrazones **423**, fol-

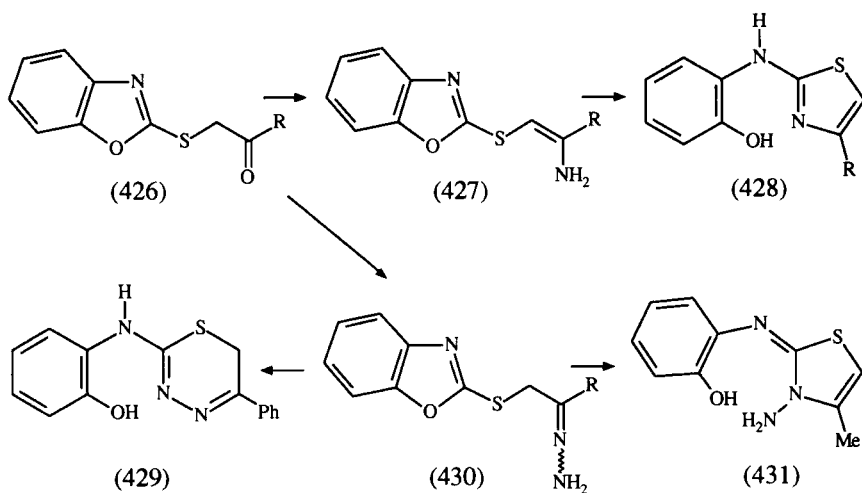


SCHEME 66

lowed by an *ipso*-attack by the side-chain with consequent oxazole ring opening and cyclodehydration of the rearranged **424** into the end products. In a similar reaction, pyrolysis of the 2-(3-aminobutyl)-4,5-diphenyloxazole, obtainable by reductive amination of the oxazolone ketone **422** (X = CH₂; R = Ph; R' = Me), affords directly 5-methyl-2,3-diphenyl-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazole [83JCS(P1)3027]. Benzoxazoles **426** react with ammonium acetate in refluxing acetic acid to give the rearranged **428** via the unisolated enamino precursors **427** (Scheme 67) (82H2119). Similarly, ketones **426** react with hydrazine hydrate in acetic acid at room temperature to produce **429** or **431**, depending on the nature of R (Me or Ph), which determines the actual attacking nitrogen in the hydrazones **430** (Scheme 67) (82H2119).

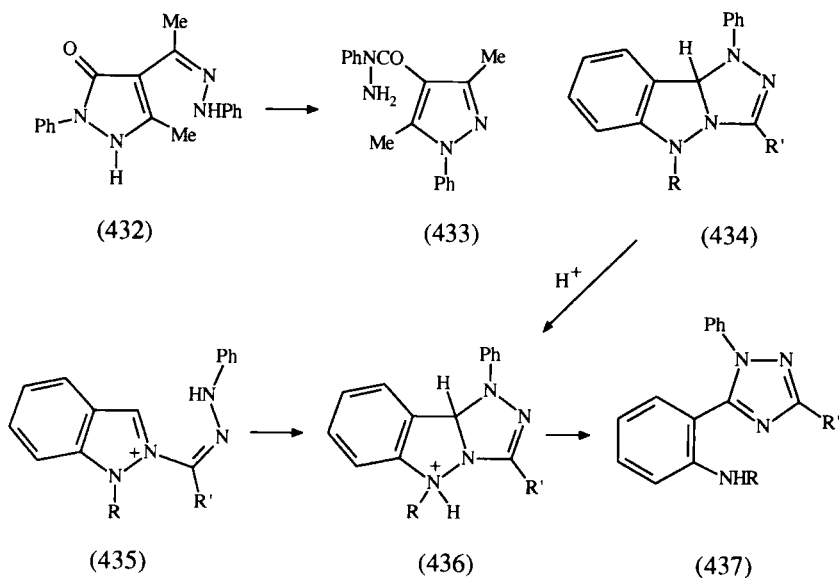
b. *Pyrazoles–Imidazoles*. The acid-induced rearrangement of the phenylhydrazone **432** yields the phenylhydrazidopyrazole **433** (78MI1), and this result allows the correction of the formerly reported structure of 1,6-diphenyl-3,4-dimethylpyrazolo[3,4-*c*]pyrazole (39JIC63). The rearrangement proceeds by nucleophilic attack of the phenylhydrazone nitrogen on C(3) of the pyrazole nucleus, with breaking of the N(2)–C(3) bond of the ring. The acid catalysis increases the electrophilicity of the pivotal carbon and favors N–C bond fission (78MI1).

The cycloadduct **434** (R = Me, R' = COMe) arising from the *N*-methylindazole and the *C*-acetyl-*N*-phenylnitrilimine, undergoes an acid-catalyzed rearrangement into the corresponding 1,2,4-triazole **437** via N–N



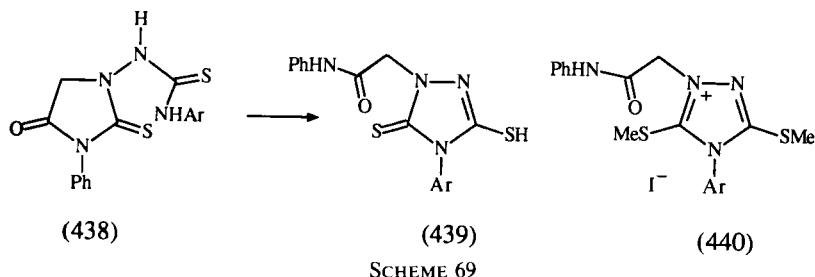
SCHEME 67

bond fission in the protonated species **436** (Scheme 68) (76H1655). By acid-catalyzed heterocyclization into the same protonated species **436**, hydrazones **435** also rearrange to triazoles **437** (78H1577). Nevertheless, this reaction does not fit our general scheme, since the bond that is breaking does not involve the C(3) pivotal center.



SCHEME 68

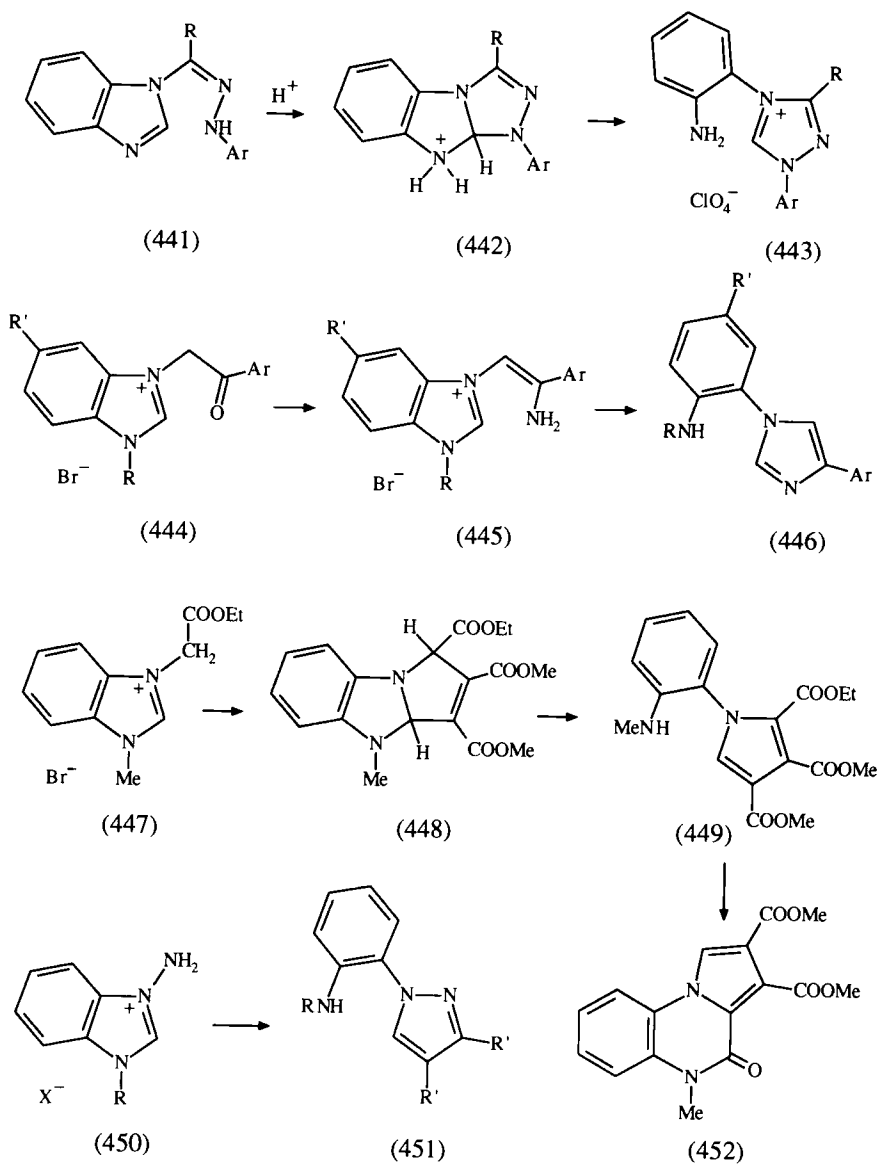
Arylthioureas **438** react with amines in refluxing ethanol to rearrange into 3-sulfhydryltriazoles **439**, which may be isolated after acidification with hydrochloric acid (Scheme 69) (89S518). A similar pathway that will



give directly the triazolium iodides **440** takes place on reacting **438** with an excess of methyl iodide in ethanol; a preliminary S-methylation at the cyclic thione group favors nucleophilic attack by the thiourea side-chain. Ring opening and a subsequent or concomitant second S-methylation explain the final products (89S518). Rearrangements involving an *ipso*-attack result from the reaction of some 2-phenacyl- Δ^2 -imidazolines with hydroxylamine hydrochloride. In this instance, spiro intermediates arising from the unisolated oximes collapse to 5-(2-aminoethylamino)isoxazoles (89S12).

Arylhydrazones of *N*-acylbenzimidazoles (**441**) react with perchloric acid to rearrange into 1,2,4-triazolium salts **443**, which can be isolated when R = Ar = Ph (Scheme 70). The protonated cycloadduct **442** represents a key intermediate. A reverse process was also pointed out: neutralization of the triazolium salt **443** (R = Ar = Ph) with aqueous sodium carbonate gives back the corresponding **441**, likely via a preliminary heterocyclization into a neutral cycloadduct. When R is a COMe or COOEt the unisolated triazolium salts **443** transform into final products by a condensation between the amino group and COMe or COOEt (89H339).

The 3-phenacylbenzimidazolium bromides **444** react with ammonium acetate in refluxing acetic acid to give imidazoles **446**; here, the enamino compounds **445** are proposed as the rearranging species (Scheme 70), whereas a possible mechanism proceeding by an initial ammonolysis of the heteroring is excluded (82CHE293). Electron-withdrawing substituents cause a reactivity increase, supported by an increase in the yields of the rearranged products. 1,2-Dimethyl-3-(*p*-nitrophenacyl)benzimidazolium bromide behaves similarly. A rearrangement proceeding by cleavage of the N(1)—C(2) bond in a benzimidazole system is also assumed in the reaction of 1-methyl-3-(ethoxycarbonylmethyl)benzimidazolium bromide



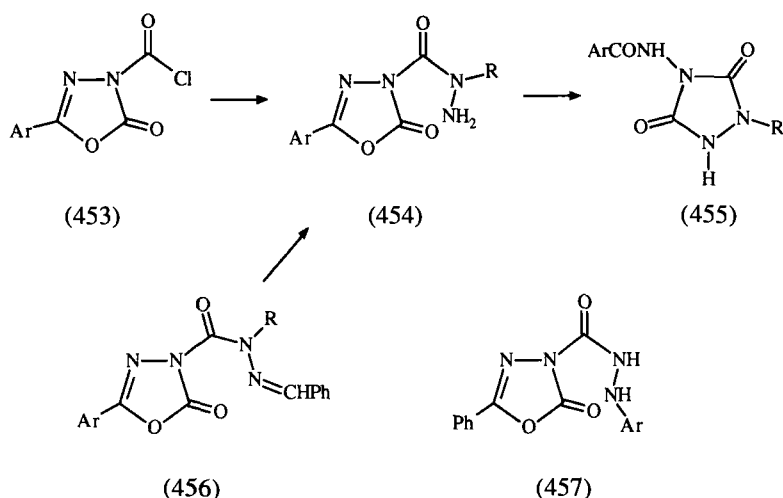
SCHEME 70

(447) with dimethyl acetylenedicarboxylate in the presence of triethylamine (75TL413). Here, the unisolated cycloadduct **448** first rearranges into the pyrrole **449**, from which the pyrroloquinoxaline **452** arises as a final product (Scheme 70). Similarly, 1-alkyl-3-aminobenzimidazolium salts (**450**) react with dimethyl acetylenedicarboxylate or dibenzoylacetylene in the presence of bases to rearrange into 1-(*ortho*-alkylaminophenyl)pyrazoles **451** ($R' = \text{COOEt}$, COPh) (Scheme 70) [73CI(L)952; 75JHC225].

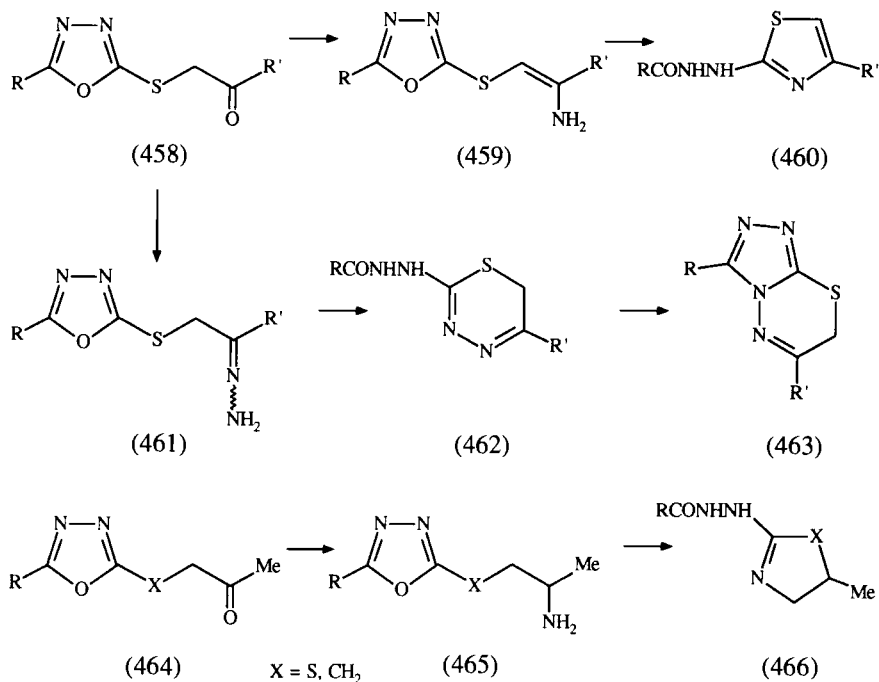
3. Five-Membered Heterocycles Containing Three or Four Heteroatoms

a. *1,3,4-Oxadiazoles*. The oxadiazole **453** ($\text{Ar} = \text{Ph}$) reacts with methylhydrazine to give the triazole **455** ($R = \text{Me}$, $\text{Ar} = \text{Ph}$) via the unisolated hydrazide **454** (Scheme 71). By contrast, arylhydrazides **457** do not rearrange. Acid hydrolysis of the benzylidenhydrazides **456** gives directly triazoles **455**; here, acid catalysis favors the rearrangement of unisolated intermediates **454** (89JHC231).

Some rearrangements in the 1,3,4-oxadiazole series are explained by an *ipso*-nucleophilic attack by the side-chain (Scheme 72). Thus, under amination conditions, oxadiazolyl ketones **458** give the rearranged thiazoles **460** via the enamino compounds **459** as intermediates. Sometimes, performing the reaction in refluxing acetic acid causes direct cyclodehydration into thiazolo[2,3-*c*]-s-triazoles. In a similar way, hydrazine in refluxing acetic acid converts compounds **458** into triazolo(3,4-*b*)thiadiazines **463**



SCHEME 71

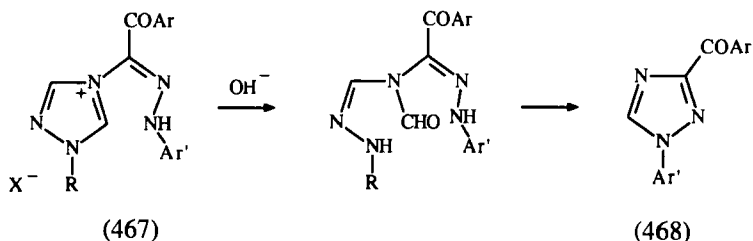


SCHEME 72

by a series of reactions including formation of **461**, rearrangement of this latter into acylhydrazines **462**, and, finally, cyclodehydration into **463** (82JOC2757). Furthermore, reductive amination of oxadiazolyl ketones **464** (X = S, CH₂) furnishes acylhydrazines **466** via the intermediates **465** (84T2703).

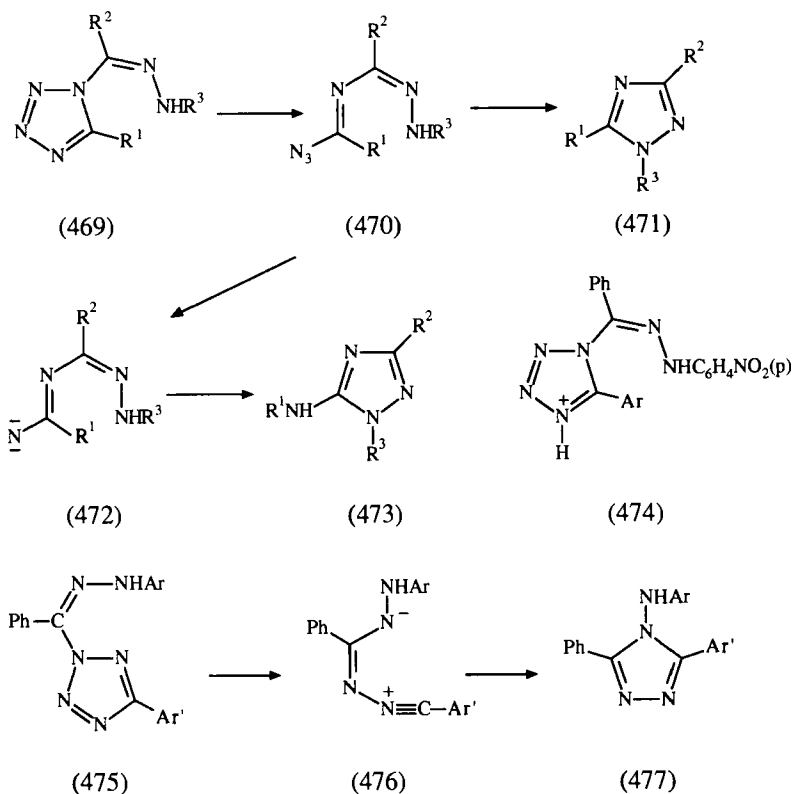
b. *Triazoles–Tetrazoles*. The base-induced transformation of aroylarylazotriazoles **467** into aroyltriazoles **468** (Scheme 73) could be framed in the usual context. However, the reaction may involve hydrolytic ring opening followed by a fragmentative heterocyclization of the former side-chain of the rearranging triazole (87MI2).

Rearrangements of 1-hydrazonoyltetrazoles **469**, which originate together with the 2-hydrazonoyl isomers in the reaction of tetrazoles and nitrilimines, are considered in Scheme 74 [86TL4921; 87BSB675; 88JCS(P1)1587]. Thermolysis of **469** in a suitable solvent assumes the intermediate formation of the azido species **470**. Subsequent fragmentative heterocyclization involves the side-chain and the azido-substituted carbon atom with displacement of hydrazoic acid to give **471** [87BSB675;



SCHEME 73

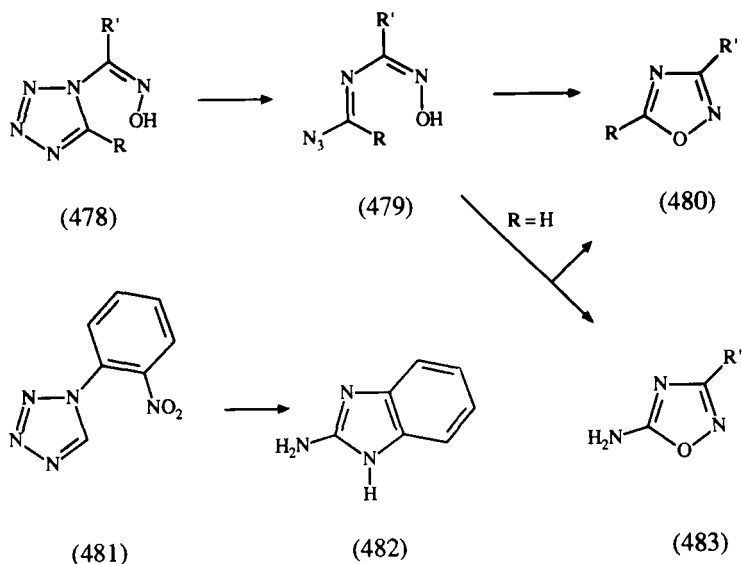
88JCS(P1)1587]. In some case, depending on substituents, a concomitant pathway proceeds via extrusion of nitrogen from the azido species **470**. In this way, the resulting nitrene **472**, and then the rearranged carbodiimide species, would explain the concomitant formation of aminotriazoles **473**



SCHEME 74

(87BSB675). Some 1-hydrazonoyltetrazoles such as **469** (R^1 = alkyl or aryl; R^2 = Ph; R^3 = *p*-nitrophenyl), which appear stable either toward thermolysis in ethanol or toward the presence of bases, undergo the rearrangement in the presence of trifluoroacetic acid. Here, protonation at N(4) of the heterocycle increases the electrophilicity of C(5), thus favoring nucleophilic attack by the arylhydrazone nitrogen, followed by breaking of the tetrazole ring. As expected, the reactivity of the protonated specie **474** will depend on the electronic effects exercised by substituents in the C(5)-aryl group. In this context, the 5-(2,6-dichlorophenyl)-substituted derivative **469** (R^1 = 2,6-dichlorophenyl; R^2 = Ph; R^3 = *p*-nitrophenyl) does not rearrange, since the orthogonal geometry between the tetrazole and the aryl ring prevents nucleophilic attack by the arylhydrazone nitrogen. Because of this, the breaking of the tetrazole ring is assumed to be subsequent to or at least concerted with nucleophilic attack by the side-chain [88JCS(P1)1587]. In a different way, thermolysis of 2-hydrazonoyltetrazoles **475** proceeds via the dipolar species **476**, from which triazoles **477** arise (Scheme 74) [88JCS(P1)1587].

Thermolysis of tetrazole oximes (**478**) in a suitable hydrocarbon solvent, or pyrolysis without it, produces 3,5-disubstituted 1,2,4-oxadiazoles (**480**) (Scheme 75) (81BSB193; 87BSB675; 91MIP137367). In the case of 5-unsubstituted tetrazoles (**478**; R = H), the reaction goes by two concomitant pathways, which imply elimination of hydrazoic acid or nitrogen.



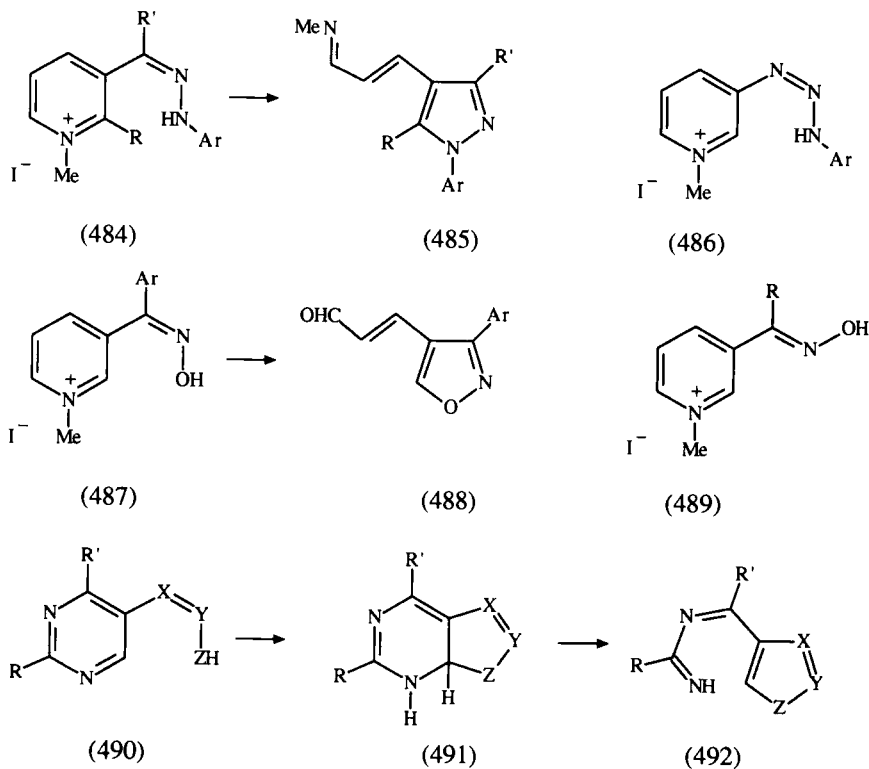
SCHEME 75

respectively, to yield both 5-unsubstituted oxadiazoles (**480**; R = H) and 5-aminooxadiazoles (**483**). As observed for 1-hydrazonoyltetrazoles, a plausible mechanism assumes ring opening of the tetrazole into the azido species **479**, from which both pathways could take place. A similar mechanism involving extrusion of nitrogen from an azido species can be envisaged in the formation of 2-aminobenzimidazole (**482**) from the reduction of the 1-(*o*-nitrophenyl)tetrazole (**481**) with sodium sulfide in aqueous ethanol (Scheme 75) (67JOC3580).

4. An Assay on the Six-Membered Heterocycles

Typical rearrangements involving a three-atoms nucleophilic side-chain are known for β -substituted pyridinium salts in which the reaction is favored by the electrophilicity of the C(2) site (Scheme 76). Arylhydrazones of 3-acylpyridinium iodides (**484**; R = H, Me) undergo a base-promoted rearrangement into methyliminopropenylpyrazoles (**485**); the reaction is explained by nucleophilic attack of the hydrazone moiety at C(2), followed by opening of the bicyclic intermediate at the pyridine level, and then by configurational isomerization of the resulting side-chain. The possible pathway that assumes a preliminary hydrolytic ring opening is discarded since the rearrangement also takes place by a reaction with nonhydrolytic bases (80CPB1265). In a similar way, aryltriazenes **486** react with aqueous sodium hydroxide to rearrange into methyliminopropenyltriazenes (80CPB2083). In the case of oxime substrates, the rearrangement is shown to depend on the geometry of the oxime group. In fact, on reacting with aqueous bases, only *Z* oximes of 3-arylpyridinium iodide (**487**) rearrange into isoxazoles **488**, whereas *E* oximes remain unchanged (80CPB2083). By contrast, oximes of the 3-acetyl- or 3-formyl-*N*-methylpyridinium iodide (**489**; R = H, Me), for which the *E* geometry is expected (75OMR524), do not rearrange (80CPB2083).

Typical rearrangements are reported for 5-substituted pyrimidines **490** (Scheme 76). The reactions generally occur in the presence of acids that enhance the electrophilicity of the pivotal carbon, and are explained in terms of a nucleophilic attack by the side-chain at C(6). The subsequent ring opening of **491** gives the rearranged **492**, from which the hydrolysis of the amidine group follows. The concerted transition state in the ring closure–ring opening process (74RTC300) has been criticized [76JCS(P1)315]. According to this generalized model, hydrazones or phenylhydrazones of 5-acylpyrimidines (**490**; XYZ = CNN) rearrange into 4-acylpyrazoles (74RTC300; 84H2013; 86JHC275; 87BSF318; 88BSF540; 89H1583; 90H1105, 90JHC1847); oximes (**490**; XYZ = CNO) rearrange into 4-acylisoxazoles (74RTC300); and *N*-(pyrimidin-5-yl)amidines (**490**;



SCHEME 76

XYZ = NCN) rearrange into 4-formylimidazoles (81JOC608). On the other hand, attempts to rearrange aryltriazenes (**490**; XYZ = NNN) into triazoles by reaction with bases or acids were unsuccessful (81JHC1639).

ACKNOWLEDGMENTS

The authors are indebted to Professor A. R. Katritzky for his encouragement and interest in this work. Financial support of the M.U.R.S.T. (Rome) in the preparation of the manuscript is gratefully acknowledged.

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Generation and Reactions of sp^2 -Carbanionic Centers in the Vicinity of Heterocyclic Nitrogen Atoms

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I. Introduction

The generation of a carbanionic center adjacent to a neutral heteroatom such as nitrogen is often a difficult proposition, and this is a consequence of several factors, of which charge repulsion by the heteroatomic lone pair, low acidity of the hydrogen to be abstracted, and undesired reaction at other reactive sites in the molecule are all major deterrents. In addition, in comparison to the more electronegative oxygen atom, or the heavier sulfur atom with its *d*-orbitals and greater polarizability, a nitrogen atom represents a weaker stabilizing group for an adjacent negative charge (87MI1). Repulsion between the lone pair of electrons and the negative charge can significantly reduce the thermodynamic stability of the system. Several different approaches have now been explored in a search for possible solutions to these problems, with the majority of these having dealt with the activation of the desired site toward deprotonation and/or the prevention of undesirable side-reactions. Although the degree of success has been quite varied, numerous methods are now available that allow carbanion formation adjacent to nitrogen with predictable ease.

The subject of saturated (*sp*³) carbanions adjacent to both heterocyclic and nonheterocyclic nitrogen has received considerable attention in the review literature in recent years [87MI1; 88PIA187; 90MI2; 91MI2, 91MI5, 92T2589], and although aspects of *sp*²-carbanion chemistry have also been discussed by several authors [87MI1, 87MI2; 88CHE117, 88KGS147, 88MI2; 89MI3; 90CRV879; 91AHC(52)187, 91MI5], there has not been the same comprehensive coverage. In this context, discussion of a number of different methods specifically developed for the synthesis and subsequent

elaboration of sp^2 -carbanions in nitrogen-containing heterocyclic systems represents the subject of this review.

A. SCOPE

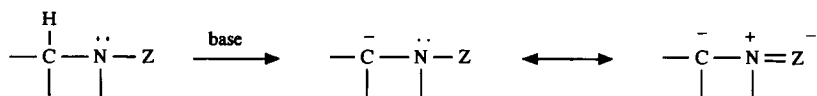
This review concentrates on the generation and subsequent reactions of two broad types of carbanion: (i) ring sp^2 -carbanions in azaheterocyclic systems, and; (ii) external sp^2 -carbanions of substituent groups adjacent to an aza-heterocycle.

Ring and substituent carbanions situated not only α -, but also β - and γ -to unsaturated (sp^2) heterocyclic nitrogen are discussed. Some of the heterocyclic systems mentioned here have also been individually reviewed elsewhere, and in these cases the present work concentrates on more recent aspects. However, earlier work is still discussed where it is felt appropriate or necessary, in order to provide a unified coverage of the subject. The greatest emphasis is placed on methods for overcoming the reluctance often shown by nitrogen heterocycles toward carbanion formation, and the direction of metalation to specific sites where more than one is available.

Heterocyclic carbanions stabilized by ylid formation, or by resonance that places the negative charge on a heteroatom, are specifically excluded. In addition, heterocyclic systems that do not depend on additional stabilization factors for their initial deprotonation, continued existence, or subsequent reaction with electrophilic substrates are discussed in less detail.

B. ACTIVATION OF AZAHETEROCYCLES TOWARD sp^2 -CARBANION FORMATION

In saturated amine systems, the hydrogen atoms adjacent to the nitrogen atom are normally not acidic enough to allow removal, even by strong bases, but if an electron-withdrawing group is attached to the nitrogen then deprotonation can often occur (Scheme 1). This process, which involves donation of the nitrogen long-pair electrons to the substituent group, is known as dipole stabilization and can be used to stabilize both internal



SCHEME 1

and external carbanions (78CRV275; 84CRV471; 88PIA187; 91MI2, 91MI5).

However, dipole stabilization is less significant as an aid to carbanion formation with unsaturated azaheterocycles, since the nitrogen lone-pair electrons are normally incorporated into the π -electron system of the heterocycle, and are therefore less readily available for donation to the substituent group. In fact, dipole-stabilization can even be a hindrance in some systems where exocyclic *sp*³-carbanion formation is competitive with internal *sp*²-carbanion formation. In these cases it is the heterocycle itself that is responsible for the dipole-stabilization of the external carbanion.

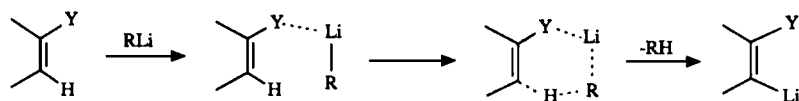
Another factor that must be considered in heterocyclic systems containing an N-H group, is that initial deprotonation always occurs on the nitrogen, and in most cases further reaction is then completely prevented. Thus, protection of the nitrogen is often essential for carbanion formation to occur. What is required is a functional group that can be added fairly readily, that is stable under the carbanion forming conditions, does not interfere with subsequent reactions with electrophiles, and which is then capable of being removed under conditions that are mild enough not to affect the remainder of the molecule. In addition, for efficient reaction it is desirable to make each of these extra steps as high yielding as possible.

Amide groups are often used to protect amino groups in normal chemical reactions, but they are much less useful in carbanion-forming reactions since nucleophilic addition of the base, and subsequent displacement of the acyl group, can readily occur under the reaction conditions. Many *N*-alkyl heterocycles can form stable carbanion derivatives, but since later removal of the alkyl group is often not possible these derivatives do not normally meet the necessary requirements. However, if there is an additional factor that favors removal, then these groups can sometimes be used. Thus, *N*-benzyl groups can be removed by hydrogenolysis or by reduction with sodium in liquid ammonia, although their utility is limited with some heterocyclic systems due to deprotonation of the exocyclic methylene group. This lateral metalation is a result of the combined effects of dipole stabilization provided by the heterocyclic ring, and resonance stabilization provided by the benzene ring.

Fortunately, however, there are a variety of amino protecting systems available that are readily introduced, are stable under the reaction conditions, and are able to be readily removed at the completion of the reaction. Discussion of the different methods that have been used successfully with individual azaheterocycles can be found in the following sections, along with an analysis of which types of protection are best to use in certain situations.

With heterocycles containing an sp^2 -nitrogen atom, a totally different problem can occur, namely nucleophilic addition of the base to the azomethine ($C=N$) bond. The use of very sterically hindered bases such as lithium tetramethylpiperidide (LiTMP) can prevent this type of addition in certain cases, but bases of this sort tend to be expensive and not suitable for general use. However, two different approaches to overcoming the problem of azomethine addition have been developed over the years, both relying on the fact that the addition is temperature dependent, and that by enabling metalation reactions to be performed at low temperatures, the desired carbanion formation can often be achieved.

The first of these two methods involves the use of halogen-metal exchange reactions (51OR339; 74M11; 87M11, 88M12), which have the advantage that they can often be performed at temperatures as low as -100°C (82ACR300). Reaction occurs specifically at the halogenated carbon, and a large variety of carbanionic derivatives have now been prepared by this route. However, a major drawback is the limited availability of the halogenated starting materials, and a more general solution occurs with the second method, which involves the removal of specific protons by direction of the added base to the desired reaction site. Thus, the presence of substituent groups containing lone-pair electrons on heteroatoms such as oxygen and nitrogen enables these groups to form coordination complexes with metal counterions such as lithium, and this can result in metalation being directed to sites adjacent to the substituent (Scheme 2)



SCHEME 2

[79OR1; 90CRV879; 91AHC(52)187]. As with halogen-metal exchange, this “complex induced proximity effect” (CIPE) (86ACR356) is able to override the normal addition of nucleophilic bases to azomethine groups, by providing a pathway for reaction to proceed at lower temperatures.

The use of metalation directing groups is not limited to those heterocyclic systems containing sp^2 -nitrogen; deprotonation can also be assisted in sp^3 -nitrogen systems. An additional bonus can also be obtained with heterocycles possessing N-H groups, since the beneficial coordinating species can be incorporated as part of the nitrogen protecting group (89MI3). In addition the CIPE process is not restricted to electron donor substituents, and aggregation of lithium atoms can be used to direct a second or subsequent metalation to a site adjacent to a previously added

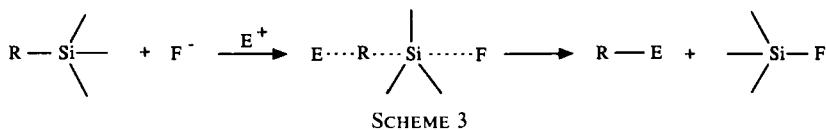
lithium counterion (83PAC355; 86ACR356). Discussion of the relative merits of the specific directing groups that have been used with different heterocyclic systems can be found in the appropriate chapters.

Finally, the primary site of reaction with some heterocyclic systems may not be one that is desired for final elaboration, and in these cases blocking of the initial reaction site is necessary. This can often be achieved by a consecutive metalation and alkylation sequence, but as with N—H protection the overall process, including final removal of the blocking group, must be achievable in reasonable yield. Trialkylsilyl groups have so far received the most attention in this area, because of their ready addition, relative stability under metalation conditions, and facile hydrolysis.

C. STABILIZATION OF AZAHETEROCYCLIC sp^2 -CARBANIONS

Several factors, often mutually complementary, may determine the favorable existence of a carbanion, but the most significant are those that lower the energy level of the carbanion. Lowering the temperature of the reaction solution is the simplest way of prolonging the lifetime of a carbanionic species, whereas lowering of the enthalpy level of the carbanion itself, indicated by a lower heat of protonation (74JA6803), can be achieved by the presence of functional groups that are capable of coordinating or internally chelating the metal counterion. These groups are often the same ones that facilitate the initial deprotonation by directed metalation (Section I,B), and thus their presence serves a dual purpose. X-ray studies [e.g., 82JA5490; 86AG(E)1103; 87AX(C)1429; 88RTC431; 89JA3463] have shown an increased lithium aggregation and a decreased carbon–metal bond length in these coordinated species, factors that are indicative of a decreased ionic character.

The relative stability of a carbanion can be affected by the availability of degradative pathways, with both heteroaryne formation with azines (82T427; 89ACR275) and the ring-cleavage reactions seen with deprotonated azoles being examples of this [87AHC(41)41]. It is sometimes possible to trap or mask the carbanion as a more stable metalloid derivative, and to release it in the presence of electrophile. Trialkylsilane and trialkylstannane derivatives have received the most attention in this area (81T4069; 88G211), since they are often able to react directly with reactive electrophiles such as acyl halides. In addition, by the use of fluoride-induced carbon-silicon bond cleavage (Scheme 3), it is sometimes possible to generate a nonbasic carbanionic species from trialkylsilanes that is capable of undergoing *in situ* addition to a variety of electrophilic sub-



strates, including relatively acidic species such as enolizable aldehydes and ketones (81T4069; 88G211). Because reaction appears to occur via a pentacoordinate organosilicon intermediate (86JOC1745) the free carbanion is never formed, and undesirable side reactions are therefore minimized.

D. ELABORATION OF AZAHETEROCYCLIC sp^2 -CARBANIONS

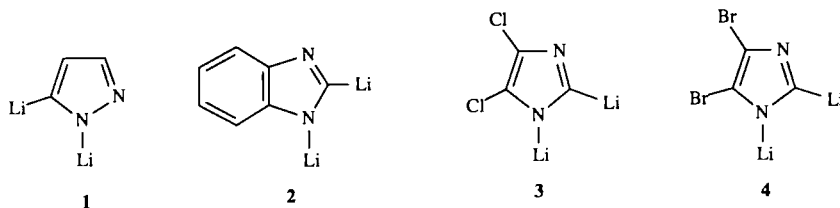
Once generated, the synthetic utility of hetero-carbanions lies in their subsequent reaction with suitable electrophiles, and since all carbanions possess both basic and nucleophilic properties, the triumph of the latter property over the former is a necessity for the overall viability of the process. The above dichotomy is largely determined by the nature of the organometallic bond, which can lie anywhere between a highly ionic and a highly covalent character, with a predominant covalent character being the preferred choice for subsequent nucleophilic processes. Increased covalency of the carbon-metal bond, and hence decreased basicity of the carbanion, can also be achieved by transmetalation to more polarizable (softer) counterions such as copper (75OR253); the use of covalently bonded metalloid derivatives has already been mentioned (Section I,C). In addition, as also previously mentioned (Section I,C), internally chelated carbanions generally possess less ionic covalent character, and are therefore less basic, than nonstabilized carbanions, and this enables them to react successfully with a wider range of electrophiles.

The various methods outlined above for increasing the viability of azaheterocyclic sp^2 -carbanions and the successful utilization of these in synthetic schemes are discussed in more detail in the following sections.

II. Ring sp^2 -Carbanions of Azoles

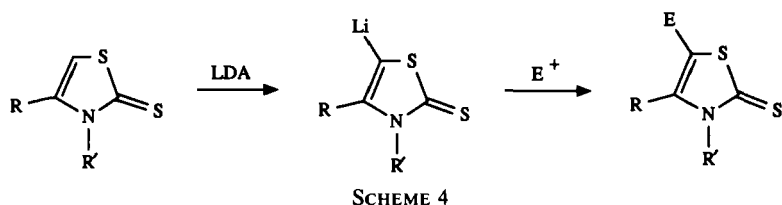
The α -metalation of azoles (aromatic nitrogen-containing five-membered rings) is a much more facile process than that for the analogous saturated systems, and a small number of heterocycles containing free NH groups can undergo some direct lithiation, despite the ionization of the

nitrogen, although the reaction with electrophiles usually occurs in quite low yields. Examples are pyrazole (59LA55) and benzimidazole (73CB2815), where product yields for reaction of the lithio species **1** and **2** with an electrophile are of the order of 9% and 17%, respectively. However, higher yields are achievable with halogen-metal exchange reactions, where the lower activation energy makes dianion formation more favorable, and thus moderate yields of 2-substituted imidazoles were obtained with the 2-lithio derivatives **3** and **4**, which were prepared from the analogous 2-bromo compounds by selective exchange [82JOC2196; 87JCS(P1)1445].



Normally, however, extra steps are required, in that it is necessary first to protect the nitrogen atom such that it cannot undergo ionization and second, following the metalation and subsequent reaction with appropriate electrophiles, to remove that protection. These extra steps involve yield losses, so it is important to make them as high yielding as possible, but also to make the removal of that protection as facile as possible in order to prevent undesirable side-reactions. Benefits can be obtained if the added group contains a heteroatom that is capable of complexing with lithium, since this can assist with both the initial deprotonation and stabilization of the resulting carbanion. A variety of different removable complexing groups are available for the protection of ionizable N—H groups in azaheterocycles, and the various approaches that have been investigated in this regard represent a major component of the following sections.

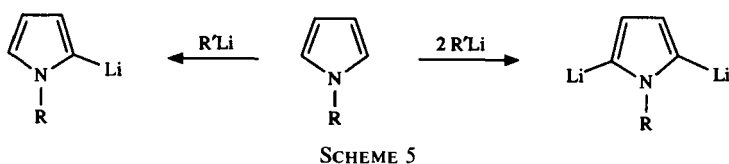
Direct metalation at the β -carbon of azoles can also occur, although it is a much less facile process than that for the adjacent α -carbon, because of the greater charge density at what is normally a nucleophilic center in enamine-type reactions. Thus in order for reaction to occur, it is usually necessary to either block the α -position or activate the β -site. If both factors are accommodated then β -metalation occurs readily, and thus 3,4-disubstituted-2(3*H*)-thiazolethiones undergo direct lithiation with lithium diisopropylamide (LDA) at the 5-position, which is activated by the inductive effect of the adjacent sulfur (Scheme 4) (80S800).



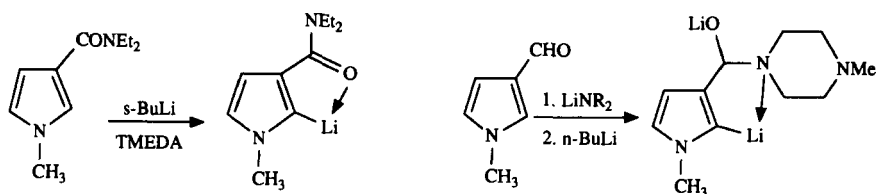
A. PYRROLES AND INDOLES

1. Pyrrole α -Carbanions

No deprotonation of carbon occurs with pyrroles unsubstituted on nitrogen, so in order for carbanion formation to occur, protection of the nitrogen is essential. However, once protected, the α -lithiation of N-substituted pyrroles occurs readily (79OR1; 84MI2), and in the case of N-methylpyrrole, both 2-mono and 2,5-dilithiation can occur, depending upon the reaction conditions (Scheme 5) [79JCS(P1)2845; 82SC231].

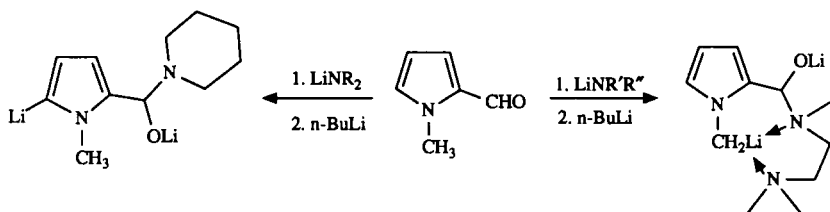


In addition to the parent heterocycle, both N,N-diethyl-1-methylpyrrole-3-carboxamide and 1-methylpyrrole-3-carboxaldehyde have been selectively α -lithiated in the 2-position (85TL6213; 87JOC104), the latter compound via the intermediacy of an α -(N-methylpiperazino) alkoxide (Scheme 6). The α -amino alkoxide is formed *in situ*, via the addition of



lithium *N*-methylpiperazide to the aldehyde group, and serves to protect the carbonyl functionality during the lithiation step, as well as being involved in directing lithiation to the adjacent α -position. The aldehyde group is easily regenerated during the workup of the one-pot reaction.

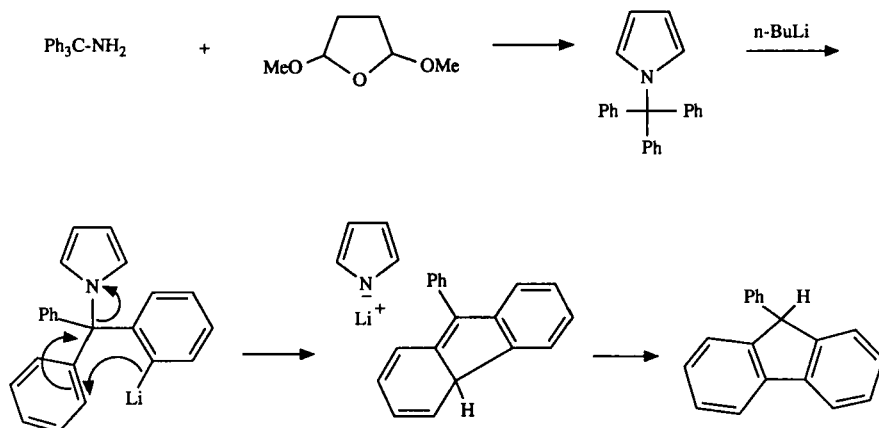
When the same reaction sequence was repeated with 1-methylpyrrole-2-carboxaldehyde, clean reaction at the 5-position was observed (87JOC104), emphasizing the strong preference for α - rather than β -metalation in the pyrrole system. Interestingly, when the amine component was changed to *N,N,N'*-trimethylethylenediamine, lithiation occurred with high regioselectivity on the *N*-methyl group (Scheme 7) (87JOC104).



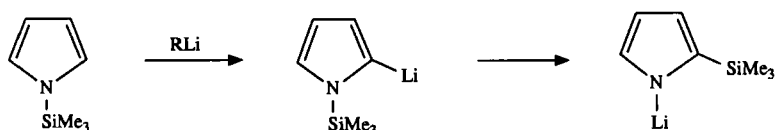
SCHEME 7

Removable protecting groups that have been investigated with the pyrrole system include benzenesulfonyl [81JOC157; 82JOM(234)123]; *tert*-butoxycarbonyl (BOC) (81JOC156); dimethylamino (81JOC3760); trialkylsilyl [82JCS(P1)1833]; [2-(trimethylsilyl)ethoxy]methyl (SEM) (83CC630; 84JOC203, 84JOC3503; 86T3723), trityl [83JCS(P1)93]; the lithium carboxylate, which is actually formed *in situ* by reaction of the pyrrole anion with carbon dioxide (88OPP585); and the *tert*-butylcarbamoyl (91S1079), which actually undergoes deprotonation to its *N*-lithio derivative under the reaction conditions. Most of these protected derivatives are formed from pyrrole itself, although two exceptions are the dimethylamino and trityl compounds, which are obtained by condensation of 2,5-dimethoxytetrahydrofuran with *unsym*-dimethylhydrazine (81JOC3760) or tritylamine, respectively [83JCS(P1)93]. The trityl derivative appears to be too hindered to undergo α -metalation, because on treatment with *n*-BuLi the isolated products are pyrrole and 9-phenylfluorene. These products are presumed to arise via an initial *ortho*-lithiation of one of the phenyl groups, followed by displacement of pyrrolyl anion during ring closure to the tricyclic compound, which then undergoes a 1,3-hydrogen shift to give the observed product (Scheme 8) [83JCS(P1)93].

α -metalation can be achieved with the *N*-trimethylsilyl derivative, and dilithiation can also be achieved under certain conditions, but a major drawback arises with this substituent due to its tendency to migrate to the



SCHEME 8



SCHEME 9

α -carbanion site to produce the thermodynamically more stable N-anion (Scheme 9) [82JCS(P1)1833].

However, α -metalation does occur successfully with all of the other protected derivatives, provided that the appropriate conditions are used (Table I).

Both the benzenesulfonyl and the *tert*-butoxycarbonyl derivatives undergo cleavage of the protecting group when *tert*-butyllithium is used as the base (entries 1 and 3) (81JOC157), but this problem is successfully overcome by the use of the more hindered lithium 2,2,6,6-tetramethylpiperidide (LiTMP) (entry 3). The SEM derivative undergoes some dilithiation on attempted mono-lithiation with *tert*-butyllithium in THF-hexane (84JOC203), but only monolithiation is reported with *n*-BuLi in dimethoxyethane (entry 5) (84JOC3503; 86T3723). Interestingly, no lithiation whatsoever was observed on treatment with *n*-BuLi in THF (84JOC203). No problems of base incompatibility or dilithiation are reported for the dimethylamino derivative (entry 4) (81JOC3760), or for the lithium carboxylate or *tert*-butylcarbamoyl groups (entries 6 and 7), where the presence of the substituent negative charge serves to prevent nucleophilic attack by the base (88OPP585; 91S1079).

TABLE I
SYNTHESIS OF 2-SUBSTITUTED PYRROLES VIA α -LITHIATION OF N-PROTECTED DERIVATIVES

Entry	R	Metalation conditions	Yield (%)	Deprotection	Yield (%)	Reference
1	SO ₂ Ph	<i>t</i> -BuLi/THF/ -80°C	80 ^a	— ^b	— ^b	81JOC157 ^c
2		LiTMP/THF/ -80°C	76 ^d	— ^b	— ^b	81JOC157
3	CO ₂ - <i>t</i> -Bu	LiTMP/THF/ -80°C	35–92 ^e	OMe ⁻	66–99	81JOC157
4	NMe ₂	<i>n</i> -BuLi/THF/ — ^f	70–80	Cr ₂ (OAc) ₄	95	81JOC3760
5	SEM ^g	<i>n</i> -BuLi/DME/ -10°C	40–64	<i>n</i> -Bu ₄ N ⁺ F ⁻	51–56	86T3723 ^h
6	CO ₂ ⁻ Li ⁺ ⁱ	<i>t</i> -BuLi/THF/ -70°C	— ^j	— ^k	50–95 ^l	88OPP585
7	CONH <i>t</i> -Bu	2 <i>t</i> -BuLi/THF/ -78°C	45–78	LiOH ^m	58–75 ⁿ	91S1079

^a Deuteration yield, product accompanied by 10–11% cleavage.

^b Deprotection not attempted.

^c See also 82JOM(234)123.

^d Deuteration yield.

^e 92% value represents recovery of 88% deuterated material.

^f Temperature not given.

^g SEM = CH₂OCH₂CH₂SiMe₃.

^h See also 83CC630, 84JOC203, and 84JOC3503.

ⁱ Formed *in situ* by reaction of lithio pyrrole with CO₂.

^j Not isolated.

^k Spontaneous loss of CO₂ on acidification during workup.

^l Overall yield.

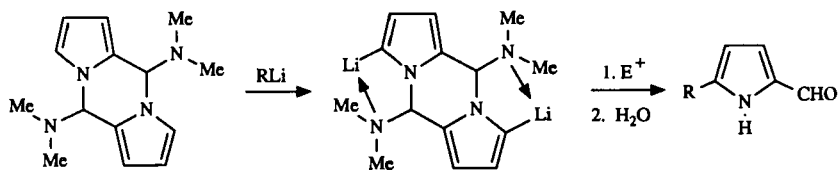
^m Spontaneous loss of substituent during workup when added substituent contained a carbonyl group.

ⁿ Overall yield for reactions where spontaneous deprotection occurred.

It is difficult to directly compare the efficacy of the various protection systems because different electrophiles have often been used in the reaction with the 2-lithio derivatives. However, some general patterns can be ascertained, and if the ease of reaction, use of inexpensive reagents, purity of the products, and ease of hydrolysis of the protecting group are all considered, then some conclusions can be made. Thus the benzenesulfonyl and *tert*-butoxycarbonyl compounds require the use of the expensive LiTMP base, but yields are good and hydrolysis facile. The dimethylamino derivative can be deprotonated with the less expensive *n*-BuLi, and the lithio species reacted in good yield with aldehydes, trimethyltin, or MgBr₂. The magnesium derivative derived from the latter reaction can in turn be

reacted with pyridinethiol esters to give acyl derivatives. Cleavage of the dimethylamino protecting group can readily be achieved with chromous acetate in very good yield (81JOC3760). The only drawback to this method would appear to be when starting with substituted pyrroles, since availability of the appropriately substituted 2,5-dimethoxytetrahydrofuran would be required. Dilithiation with the SEM group can be avoided by the appropriate choice of conditions, but the use of this group would appear to be limited by both moderate reaction and hydrolysis yields. The lithium carboxylate appears to suffer from few of the above problems, with good to excellent product yields being obtained, hydrolysis occurring spontaneously and quantitatively during workup of the reaction. The protecting group is conveniently added *in situ*, and this route is probably the method of choice, except where retention of the protecting group is desired for subsequent steps. The *tert*-butylcarbamoyl group can similarly be added *in situ* if desired, and therefore it appears to offer promise as an alternative to the carboxylate group in some cases.

In addition to the protected pyrroles mentioned above, the 1-azafulvene dimer formed by Mannich reaction of pyrrole-2-carboxaldehyde with dimethylamine has also been successfully lithiated adjacent to both pyrrole nitrogens (Scheme 10). Reaction with electrophiles and subsequent hydrolysis leads to 5-substituted pyrrole-2-carboxaldehydes in good yield [88TL777; 92JOM(423)173].

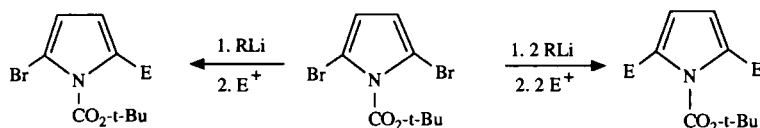


SCHEME 10

As yet, no one has investigated the use of animal protecting groups for pyrrole itself, but this is probably not worth pursuing, since the only viable route to this type of compound appears to be via quaternization and rearrangement of the *N*-dimethylamino compound (83HCA1860).

Halogen-metal exchange can also be used as a route to 2-lithiated pyrroles, and because this process can be achieved at much lower temperatures than direct metalation it is now possible to use the *t*-BOC protecting group with *n*-butyllithium (87TL6025). 2,5-dilithiation can also be achieved using this system, and the two bromine atoms in 1-*tert*-butoxycarbonyl-2,5-dibromopyrrole can both be replaced to give symmetrical products,

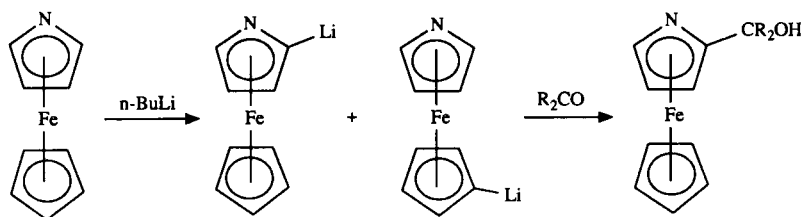
or only one replaced to give 5-substituted 2-bromopyrroles (Scheme 11) (87TL6025; 91S613).



SCHEME 11

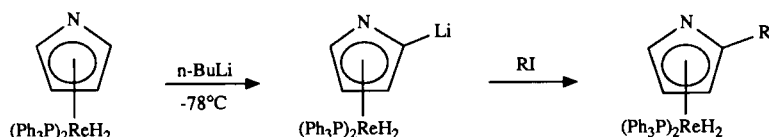
Although it was not attempted, the second bromine atom could presumably have been replaced by a second lithiation step prior to the hydrolysis, thereby giving rise to a variety of unsymmetrical 2,5-disubstituted pyrroles.

Metal complexes of pyrrole have also been investigated as substrates for lithiation reactions, with both iron and rhenium η^5 -pyrrole derivatives having been found to undergo α -lithiation [90H(31)383]. Azaferrocene was the first derivative of this type to be studied [83JOM(251)C41], but it was found that lithiation was not selective and occurred equally in both rings. However, notwithstanding this, it has recently been reported that isomerically clean products can be obtained in certain circumstances from reaction with certain carbonyl compounds (Scheme 12) (89MI2).



SCHEME 12

Competitive lithiation cannot occur with monocyclic compounds, and clean α -lithiation was observed with the rhenium bis-(triphenylphosphine) dihydro complex at -78°C (Scheme 13) [89JOM(362)C31; 90H(31)383]. So far, only reaction with alkyl halides has been reported, but presumably other electrophiles would react similarly.

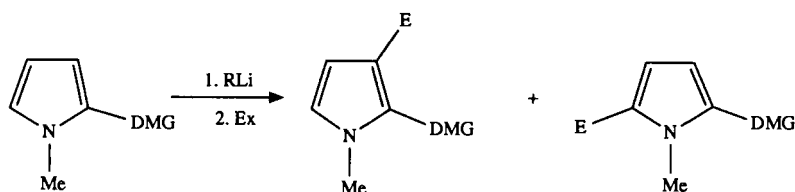


SCHEME 13

The attraction of the rhenium system is that deprotection of the pyrrole can readily be achieved by treatment with acid and DMSO, which replaces the kinetically labile η^5 -pyrrole ligand on the metal [87JOM(326)C17; 90H(31)383]. However, the relatively high cost of rhenium will almost certainly preclude its synthetic use as a pyrrole protecting group, especially when compared with the alternative methods discussed above.

2. Pyrrole β -Carbanions

Pyrroles normally undergo electrophilic substitution at the 2-position, so methods able to overcome this tendency and produce 3-substituted derivatives are of synthetic importance (85S353). Lithiation of *N*-methylpyrroles containing directing substituents in the 2-position can give moderate yields of 2,3-disubstituted derivatives [82JCS(P1)1343; 85JOC4362], but often mixtures of products are obtained, arising from competitive α -lithiation at the 5-position (Scheme 14) [82JCS(P1)1343; 85JOC4362, 85T3803].

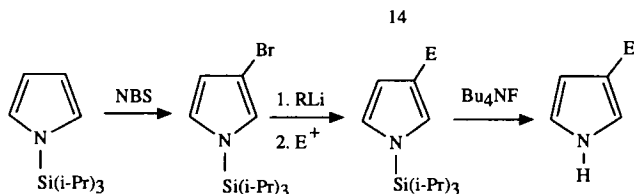


DMG = 4,4-dimethyl-2-oxazoline or CONH-*t*-Bu or *N,N'*-dimethylimidazolidine

SCHEME 14

No examples of directed β -metalation of pyrroles containing removable *N*-substituents are available, and alternative approaches have so far failed to give clean reaction products. Thus, while β -lithiation was the predominant mode of reaction with *N*-trimethylsilylpyrrole and *t*-BuLi [82JCS(P1)1833], several other products were also obtained. As an alternative to the above limitations however, halogen-metal exchange reactions on 3-halopyrroles have been found to be an excellent solution. Indeed halogen-metal exchange at the 3-position of pyrroles is so facile that it has even been performed on an *N*-unsubstituted pyrrole in the presence of an ester function (85JOC425; 88JOC976). An early use of the halide replacement method involved 1-benzyl-3-bromopyrrole and lithium metal (67CJC2227), but although a good yield of the 3-carboxylic acid was obtained, debenzylation could not be achieved with Raney nickel and hydro-

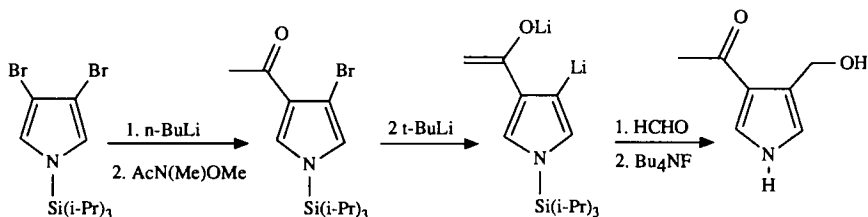
gen under pressure. No attempt was made to use sodium in liquid ammonia, conditions that are successful with other *N*-benzyl heterocycles. Much better results have been achieved with 3-bromo-1-(triisopropylsilyl)pyrrole) (Scheme 15), and good yields of 3-substituted pyrroles can



SCHEME 15

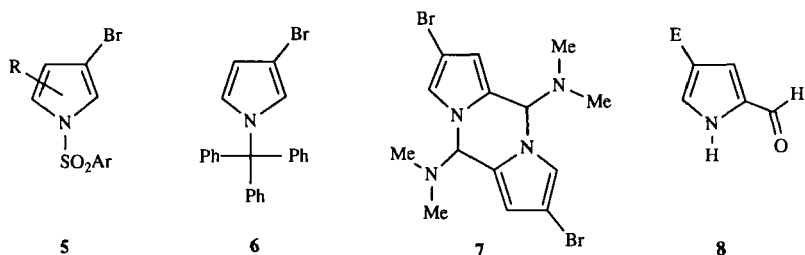
be achieved after desilylation with tetrabutylammonium fluoride [84HCA1168, 84JOC3239; 86MI1; 89CB169, 89H(29)79, 89JA6228; 90JOC6317]. Recently the analogous 3-iodo-1-(triisopropylsilyl)pyrrole has also been utilized as a source of the lithio derivative (92JOC1653). In only one case has a low yield been reported with this method (90MI5), but that result was more due to the nature of the electrophile used than to the method itself.

The same methodology can also be used for the sequential replacement of the two bromine atoms in 3,4-dibromo-1-(triisopropylsilyl)pyrrole, and a variety of different disubstituted derivatives have now been prepared (84HCA1168; 90TL6785). An example is shown by the synthesis of verrucarin E (Scheme 16) (84HCA1168; 90JOC6317).



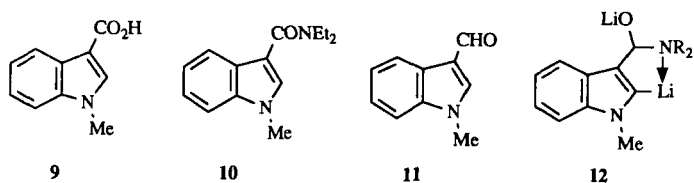
SCHEME 16

Other examples of *N*-substituted 3-bromopyrroles that have been successfully derivatized at the 3-position include either 4- or 5-substituted-3-bromo-1-tosylpyrroles **5** (90TL6785; 91T7615); 3-bromo-1-tritylpyrrole **6** (91UPI); and the bromo-azafulvene dimer **7**, which leads to 4-substituted pyrrole-2-carboxaldehydes **8** after reaction with electrophiles and hydrolysis (88TL3215).

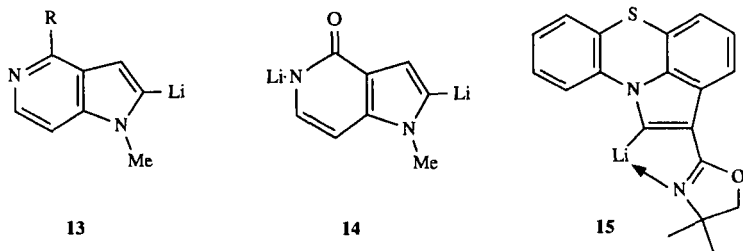


3. Indole α -Carbanions

As with pyrrole, the α -lithiation of *N*-substituted indoles occurs readily [79OR1; 84M12], and reaction can also be performed in the presence of a number of reactive functional groups at C-3. Thus the 3-carboxylic acid, 3-diethylamide, and 3-aldehyde derivatives of *N*-methylindole (**9**, **10**, and **11**) have all been α -lithiated (87JOC104; 91M17), the latter via its α -(*N*-methylpiperazino) alkoxide **12**.



Azaindole derivatives similarly undergo lithiation at C-2, and examples include both 4-substituted and 4,5-dihydro-4-oxopyrrolo[3,2-*c*]pyridines **13** and **14** [83T1777; 91JCS(P1)3173]. Lithiated polycyclic indole derivatives such as the pyrrolo[3,2,1-*k*]phenothiazine **15** can also be formed, but in this case the dimethyloxazoline group is necessary to ensure selective reaction in the 5-membered ring (83H641). Thus in the absence of the oxazoline group, competitive β -metalation also occurs at the unsubstituted ortho position of the benzene ring (83H33).



Since normal electrophilic addition to indoles occurs at the 3-position, the lithiation of compounds containing removable N-substituents has received a lot of attention over the years, because of its importance as a route to 2-substituted indoles. As a result, a variety of different protection systems are now available as shown in Table II.

TABLE II
SYNTHESIS OF 2-SUBSTITUTED INDOLES VIA α -LITHIATION OF N-PROTECTED DERIVATIVES

Entry	R	Metalation conditions	Yield (%)	Deprotection	Yield (%)	Reference
1	CH ₂ OMe	<i>n</i> -BuLi/Et ₂ O/ - 78°C → RT	40–84	BF ₃ /Br ⁻ /AC ₂ O ^a	86	73JOC3324
2	SO ₂ Ph	<i>t</i> -BuLi/THF/ - 12°C	32–75 ^b	OH ⁻ /MeOH	80–95	73JOC3324 ^c
3		LDA/THF/0°C → RT	50–81	— ^d	— ^d	81JOC2979
4		LDA/THF/ - 78°C	47–98	— ^d	— ^d	82JOC757 ^c
5	CO ₂ - <i>t</i> -Bu	<i>t</i> -BuLi/THF/ - 78°C	66–100	OMe ⁻	ca. 85	81JOC157 ^f
6	CO ₂ ⁻ Li ⁺ ^g	<i>t</i> -BuLi/THF/ - 70 → 0°C	— ^h	Δ ⁱ	52–86 ^j	85TL5935 ^j
7	SEM ^k	<i>n</i> -BuLi/DME/ - 10°C	57–70	<i>n</i> -Bu ₄ N ⁺ F ⁻	78 ^l	86T3723 ^m
8	CH ₂ NMe ₂	<i>n</i> -BuLi/THF/0°C	56–71	NaOMe	79 ⁿ	89H(29)849
9		<i>n</i> -BuLi/THF/ - 78 → 0°C	51–87	NaBH ₄ /EtOH	51–71	90JOC3688
10	OMe	<i>n</i> -BuLi/THF/ - 10°C	60–90	H ₂ /Pd/C	79–97	91H221
11	CONH <i>t</i> -Bu	2 <i>t</i> -BuLi/THF/ - 78°C	70–98	LiOH ^o	70–85 ^p	91S1079
12	2-Oxazoline	<i>n</i> -BuLi/THF/ - 80°C	20–31 ^q	OH ⁻ /EtOH	83 ^r	92H(33)173

^a Aqueous HCl unsuccessful.

^b Isolated yields of 22–36% were obtained in those cases where substituent cleavage also occurred.

^c See also 76JOC163 and 81JHC807.

^d Deprotection not attempted.

^e See also 85H1277, 86T2389, and 90M11.

^f See also 82JOC5258 and 85JHC505.

^g Formed *in situ* by reaction of lithioindole with carbon dioxide.

^h Isolated crude material decarboxylated directly.

ⁱ Decarboxylation step quantitative.

^j See also 88SC1151, 88TL2993, 89T5955, 92JOC2495, and 92T759.

^k SEM = CH₂OCH₂CH₂SiMe₃.

^l One example only.

^m See also 89T5955.

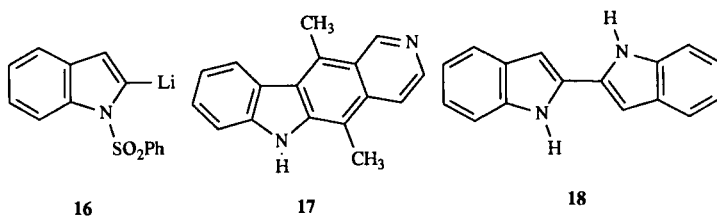
ⁿ One example only; hydrolysis unsuccessful in most cases.

^o Spontaneous loss of substituent during workup when added substituent contained a carbonyl group.

^p Overall yield for reactions where deprotection occurred.

^q 80% yield achieved in reaction with allyl bromide after transmetalation with CuBr · SMe₂.

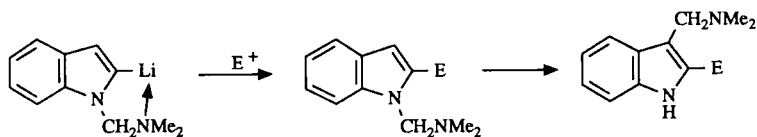
Removable *N*-substituents initially investigated included methoxymethyl, benzyloxymethyl, benzyl, benzenesulfonyl, trimethylsilyl, and *tert*-butyldimethylsilyl (73JOC3324). The best lithiation results were observed with the methoxymethyl and benzenesulfonyl groups (entries 1–4), but because hydrolysis of the former group is difficult, derivatives of *N*-benzenesulfonyl-2-lithioindole **17** were to become the intermediates of choice for many synthetic transformations. Interestingly, the substituent displacement that was seen with the pyrrole analog (Table I, entry 1) is much less of a problem in the indole case. Lithiation at C-2 is favored more strongly than with an *N*-methyl group, and selectively can be achieved in the presence of either a C-5 or a C-6 methoxy group (76JOC163). The initial work with the benzenesulfonyl compounds was performed using *t*-BuLi or *n*-BuLi as base (73JOC3324; 76JOC163), but care must be taken with these systems since a second lithiation can occur at the 2-position of the phenyl group (81JHC807). The use of LDA as the base appears to overcome this problem and gives rise to significantly improved product yields in some cases (81JOC2979; 82JOC757). Derivatives of *N*-benzenesulfonyl-2-lithioindole **16** have now been used to synthesize a large variety of compounds [e.g., 78TL5157; 80CC1241, 80JOC3382; 81JCS(P1)3008; 82JOC757; 88T3195, 88T5215; 89JOC4350; 90JMC749], with a major use being in the synthesis of analogs of the antitumor pyridocarbazole alkaloid ellipticine **17**, an area that has been well reviewed (85H1277; 86T2389; 90MI1, 90MI4; 91MI6). Transmetalation of the 2-lithio derivative **16** with copper has also been achieved (80T1439), and 2,2'-biindolyl **18** has been produced via this route.



However, because of its requirements for low temperatures and susceptibility to nucleophilic cleavage [89H(29)849], poor reactivity with certain electrophiles (85JHC505), and necessity for basic hydrolysis (81JOC157), reservations about the *N*-benzenesulfonyl group [or its tosyl analog (89JHC1869)] were expressed by a number of authors, and therefore the search for other suitable indole protecting groups has continued. Thus, in addition to those compounds mentioned above, new protected indoles that have been studied include the *tert*-butoxycarbonyl (81JOC157; 82JOC5258; 85JHC505), SEM (85JHC505; 86T3723), lithium carboxylate

(85TL5935; 88SC1151; 92JOC2495), dimethylaminomethyl [89H(29)849; 90JOC3688], methoxy (91H221), *tert*-butylcarbonyl (91S1079), and 2-oxazoliny derivatives [92H(33)173] (see Table II).

Like the benzenesulfonyl group, the *tert*-butoxycarbonyl group is less prone to nucleophilic displacement when attached to indole than to pyrrole, and *tert*-butyllithium can now be used as the base (entry 5) (81JOC157). The lithium carboxylate (entry 6) lithiates readily with *n*- or *t*-butyllithium and moderate to good product yields can be obtained (85TL5935; 88SC1151; 92JOC2495). In some cases hydrolysis is not as facile as it was with pyrrole (88OPP585) as gentle heating is now required, although it still occurs quantitatively. [The carboxylate protecting method has also been used with the analogous η^6 -indoletricarbonylchromium (0) complex, and an 83% yield of the 2-trimethylsilyl derivative was obtained (89T5955). Decarboxylation was much more facile than for uncomplexed indole.] The SEM derivative (entry 7) gives consistently better reaction yields than the analogous pyrrole, but when combined with losses during deprotection with anhydrous tetra-*n*-butylammonium fluoride, overall yields are moderate. Decomposition of the lithiated species has also been reported (85JHC505). Use of the dimethylamino substituent group (entries 8 and 9) results in efficient lithiation at C-2, and a variety of 2-substituted isogramines can be isolated in good yield [89H(29)849; 90JOC3688]. Removal of the protecting group can be achieved with sodium methoxide in methanol in the case of 2-carbonyl derivatives [89H(29)849], and with NaBH_4 in ethanol in other cases (90JOC3688). Rearrangement from the isogramine to the gramine system is sometimes observed (Scheme 17), and although



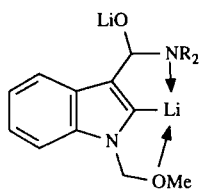
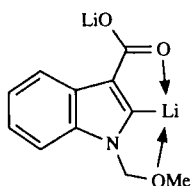
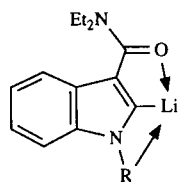
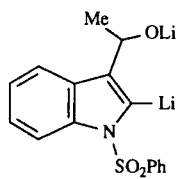
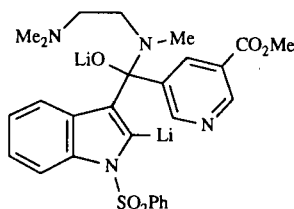
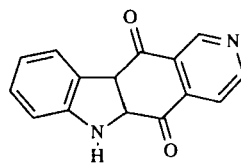
SCHEME 17

this is a disadvantage when either the isogramine or the free indole is desired, it can serve as a synthetically useful route to gramine derivatives.

The methoxy derivative (entry 10) can be lithiated readily with *n*-BuLi at -10°C and reacted with various electrophiles in very good yield, with removal of the methoxy group similarly being achieved in good yield by catalytic hydrogenation. However, the main drawback to this route would appear to be in the extra steps required in the synthesis of the starting material, which involves the oxidation of 2,3-dihydroindole with sodium tungstate, and subsequent alkylation with dimethylsulfate (91H221). The

tert-butylcarbamoyl substituent (entry 11) is easily introduced and results in good product yields, with hydrolysis being achieved either spontaneously or under mild basic conditions. Finally, the 2-oxazoline substituent (entry 12) appears to offer no advantages over the earlier groups in that several steps are required for synthesis of the protected indole and overall reaction yields are not high [92H(33)173].

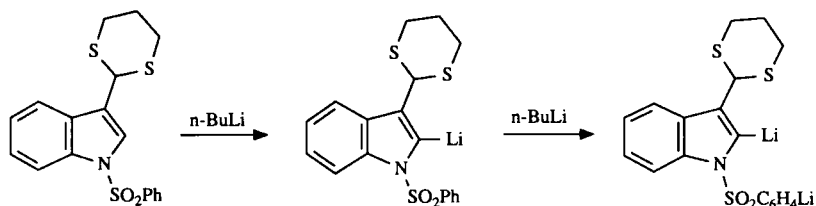
Comins and Killpack have also investigated the lithiation of a small number of *N*-protected indole-3-carboxaldehydes, using lithium *N*-methylpiperazide to form the α -amino alkoxide, and found that decomposition occurred with the *N*-benzenesulfonyl, *N-tert*-butoxycarbonyl, and *N*-dimethylcarbamyl derivatives (87JOC104). Success was achieved with the *N*-methoxymethyl derivative **19**, although no attempt was made to subsequently remove the normally difficult to hydrolyze methoxymethyl protecting group. Therefore the real viability of this method as a route to 2-substituted indole-3-carboxaldehydes cannot be judged. The 2-lithio *N*-methoxymethyl derivatives of the 3-carboxylic acid and 3-diethylamide (**20** and **21**) have also been investigated as routes to 2-substituted indole-3-carboxylic acids, but for a number of reasons, including higher reaction yields and ease of deprotection, the best overall results were achieved with the *N*-benzenesulfonyl derivative of the 3-diethylamide **22** (91MI7).

**19****20****21** R = CH₂OMe; **22** R = SO₂Ph**23****24****25**

Other 1-benzenesulfonyl-2-lithio-3-substituted indoles to have been successfully prepared include the 3-lithioxyalkyl derivatives **23** and **24** (84JOC4518; 85JOC5451), with the latter compound undergoing rapid in-

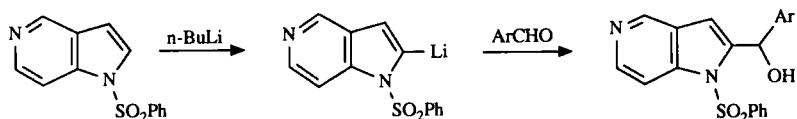
tramolecular condensation to give the ellipticine precursor **25** in 47% overall yield.

Exclusive C-2 lithiation was also observed in the case of the 1-benzenesulfonyl-3-(1,3-dithian-2-yl) derivative, but when an excess of *n*-BuLi was employed, in an attempt to promote deprotonation in the dithiane ring, ortho-lithiation of the phenyl substituent was observed forming instead (Scheme 18) (91T7911).



SCHEME 18

The benzenesulfonyl substituent has also been used in conjunction with the lithiation of an azaindole derivative (86FRP2574406; 89FRP26274931), and thus 1-benzenesulfonyl-1*H*-pyrrolo[3,2-*c*]pyridine was able to be successfully lithiated and alkylated with *p*-methoxybenzaldehyde, although reaction with more hindered ketones could not be achieved (Scheme 19) [91JCS(P1)3173].



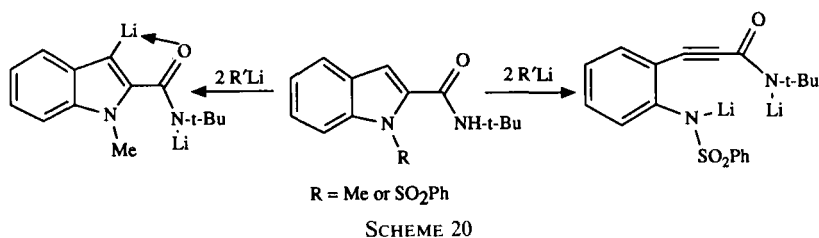
SCHEME 19

Thus in summary, a variety of different protection systems have now been developed for the α -lithiation of the indole system, with the methods available being more numerous than for pyrrole. The method chosen in a particular case will depend on the compatibility requirements of the synthetic scheme being investigated, but if immediate removal of the protecting group is desired, then the lithium carboxylate appears to be the best choice. However, if continued protection through subsequent transformations is required, then the benzenesulfonyl, *tert*-butoxycarbonyl, dimethylaminomethyl, or methoxy groups appear more suitable. Failure has been reported with both the *tert*-butoxycarbonyl and the lithium carboxylate derivatives of 3-hexylindole (91G499), presumably as a result of

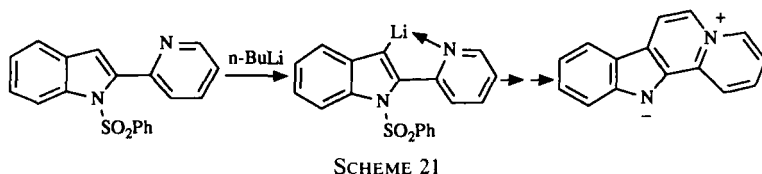
steric factors, although success has been achieved using the latter protecting group and 3-methylindole (88SC1151).

4. Indole β -Carbanions

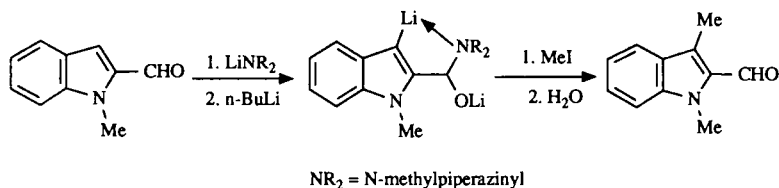
Directed β -lithiation of *N*-substituted indoles at the 3-position has been achieved with some 2-substituted indoles. Thus for example, *N*-*t*-Bu-1-methylindole-2-carboxamide can be lithiated at C-3 with *s*-BuLi and TMEDA, but when a similar reaction was attempted with the 1-benzenesulfonyl analog, cleavage to an acetylene occurred readily, even at -78°C (Scheme 20)(86H2127).



A similar cleavage reaction was observed with the 2-(1,3-dithiane-2-yl) derivative (88T443), although the same was not true of a 2-pyridyl substituent, and thus 1-benzenesulfonyl-2-(2-pyridinyl)indole was found to give a 3-lithio species which was quite stable at -78°C , only undergoing cleavage to an acetylene at 50°C (86H2127). Reaction of the 3-lithio species with electrophiles occurs in good yield (86H2127), and this method has now been used successfully in the synthesis of zwitterionic indole alkaloids related to the indolo[2,3-*a*]quinolizine ring system (Scheme 21)(87TL5259; 88T3195).



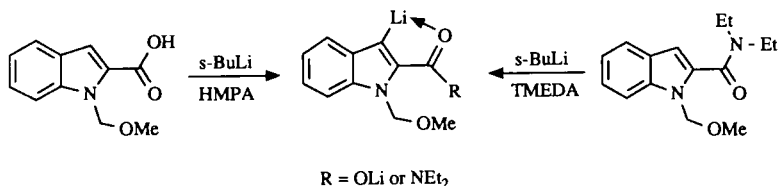
N-Methylindole-2-carboxaldehyde also undergoes β -lithiation, after *in situ* conversion to its α -amino alkoxide with lithium *N*-methylpiperazide, and the resulting 3-lithio species has been successfully alkylated with methyl iodide (Scheme 22)(87JOC104). However, when the same reaction was repeated using *N,N,N'*-trimethylethylenediamine as the amine com-



SCHEME 22

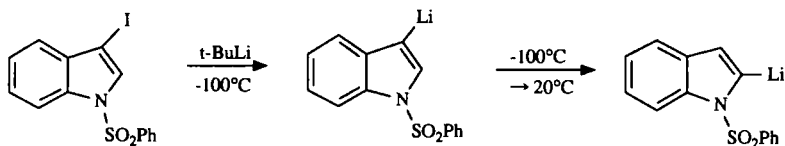
ponent, a mixture of products was obtained, resulting from metalation at both the 3-position and the *N*-methyl group.

Methoxymethyl protection of the indole NH group has also been investigated in conjunction with lithio directing 2-substituents, and compounds successfully lithiated at the 3-position have included the 2-carboxylic acid [89H(29)1661], and the related diethylcarboxamide (Scheme 23) (90PAC2047).



SCHEME 23

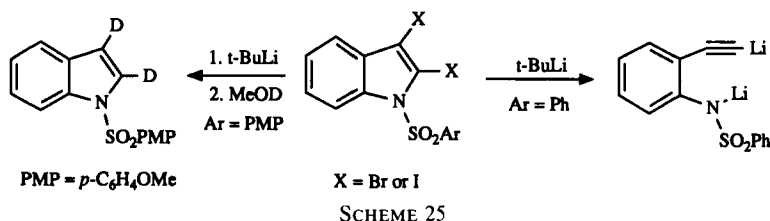
As with pyrrole, halogen-metal exchange reactions also provide a very good route to 3-substituted indoles, and the initial studies on the β -lithiation of indole concentrated on this method, with the 1-phenylsulfonyl group, so often used for protection during the α -lithiation of indoles. Thus 1-phenylsulfonyl-3-iodoindole was found to give the desired 3-lithio derivative in essentially quantitative yield at -100°C , although on warming to room temperature complete rearrangement to the thermodynamically more stable 2-isomer was observed (Scheme 24)(82JOC757).



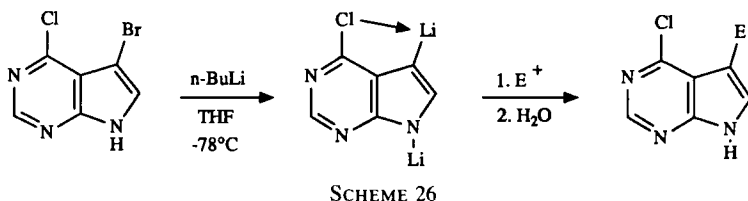
SCHEME 24

The 3-lithio species has also been generated from the analogous 3-bromo compound [85JOC5900; 90H(30)627] and has now been successfully used in the synthesis of a number of natural products (83JOC2690; 85JOC5900).

Attempts at extending the utility of the system, by double halogen-metal exchange on 2,3-diodo-(1-phenylsulfonyl)indole, were initially unsuccessful, with rapid cleavage to the acetylene occurring even at -100°C (83JOC607). More recently, however, a different result has been achieved by the use of a *p*-methoxyphenylsulfonyl (PMP) protecting group, with a 79% yield of the 2,3-dideutero derivative being obtained after treatment of the protected dibromoindole with *tert*-butyllithium (Scheme 25)(91MI6).

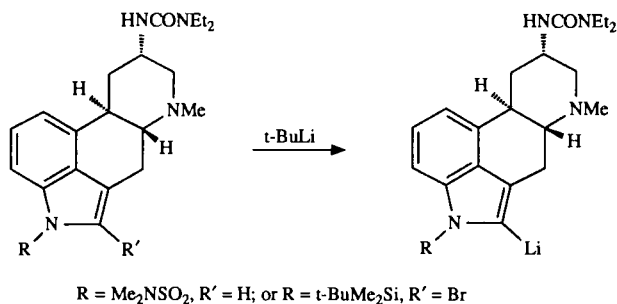


Halogen-metal exchange has also been performed in the absence of an N-substituent, as was shown by the lithiation and derivatization of the diaza derivative 5-bromo-4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (Scheme 26)(90JMC1984).



5. Ergoline Carbanions

Lithiation of an ergoline derivative containing a dimethylaminosulfonyl group on the indolic nitrogen has been found to occur at the adjacent 2-position (Scheme 27)(88TL6429). In contrast, when the more sterically hindered *tert*-butyldimethylsilyl group was used as the nitrogen protecting group, lithiation at C-2 did not occur, but instead deprotonation of the benzylic hydrogen at C-10 was observed (88TL6429). The 2-lithio derivative could be obtained by bromine-lithium exchange, however, and was found to be stable at -78°C (88TL6425), although migration of the silyl substituent to the 2-position did occur at -20°C . Reaction with a variety of electrophiles occurred successfully at the lower temperature (88TL6425), a



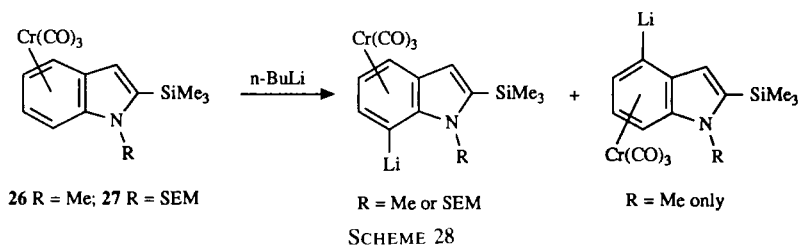
SCHEME 27

result that is different from the situation with the *N*-dimethylaminosulfonyl group where reaction could only be achieved with reactive electrophiles (88TL6429), presumably due to the electron withdrawing nature of the *N*-substituent.

B. INDOLES AND CARBAZOLES IN A FUSED BENZO RING

1. Adjacent to Nitrogen

The direct lithiation of benzo fused heterocyclic systems in the benzo ring is often less easy than in the heterocyclic ring or even at a substituent phenyl group. Thus, while *N*-phenyl indole undergoes lithiation at both the 2- and the 2'-positions, β -lithiation at the 7-position does not occur. The first observation of lithiation at the 7-position of an indole derivative was seen with tricarbonyl(η^6 -1-methyl-2-trimethylsilylindole)chromium(0) **26**, even though the major site of reaction was at C-4 (Scheme 28)

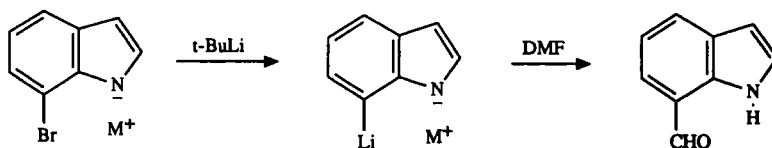


SCHEME 28

(81CC1260). However, sole reaction at the C-7 position did occur with **27** where the *N*-methyl group was replaced with a SEM group (89T5955). Reaction also occurred cleanly at the C-7 position in the absence of the

C-2 trimethylsilyl (TMS) blocking group, provided that a methyl substituent was present at the C-3 position, and this result was interpreted as being due to steric inhibition of metalation at C-2 (89T5955). In the absence of any substituents at either C-2 or C-3, mixtures of products, resulting from reaction at both C-2 and C-7, were obtained. This latter result confirms the activating effect of the chromium tricarbonyl group, since in the absence of this group *N*-SEM indole gives exclusively the products of lithiation at C-2 (86T3723).

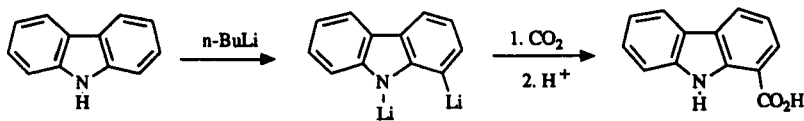
Halogen-metal exchange has also been used to produce 7-substituted indole derivatives, (Scheme 29) with the potassium salt of 7-bromoindole



SCHEME 29

giving a 61% yield of the 7-formyl indole after sequential reaction with *t*-BuLi and DMF (86JOC5106), while more recently the yield of this reaction has been raised to 73% using *n*-BuLi with the lithium salt (92SL79). In both cases the presence of the negative charge in the azole ring prevented α -lithiation from occurring at the 2-position.

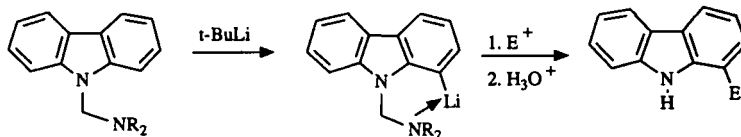
One of the earliest azaheterocyclic systems to be investigated for reaction with *n*-BuLi was carbazole, but only a very poor yield of the 1-carboxylic acid was obtained after treatment with carbon dioxide (Scheme 30)(36JOC146).



SCHEME 30

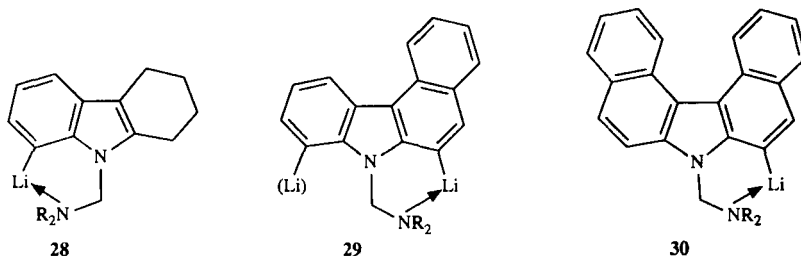
A better result was seen with the *N*-ethyl derivative, although the yield of the 1-carboxylic acid derivative was still not very high (36JOC146; 58JOC1476), whereas a different result was obtained with the analogous *N*-methyl derivative, which gave a very poor yield due to 1,8-dilithiation also occurring (52JOC860). Interestingly, a very good yield of the 1-deuterated derivative was reported after reaction of carbazole with *n*-BuLi and D₂O (84JHC837), but so far no other electrophile has been found to give a similar result. However, in marked contrast to the results seen with

carbazole itself, successful lithiation and subsequent reaction with a variety of electrophiles has been achieved with *N*-dialkylaminomethyl (aminal) derivatives (Scheme 31)(88JOC794).

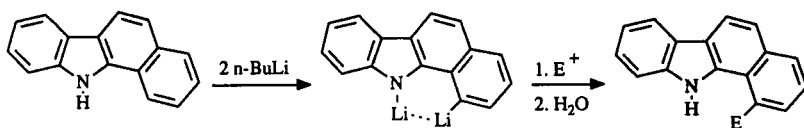


SCHEME 31

A strong solvent effect is observed for the lithiation step, with polar solvents being disfavored due to competitive coordination to the *t*-BuLi, but once lithiation has been achieved, polar solvents have no further detrimental effect, but rather aid the subsequent reaction with electrophiles by increasing the solubility of the lithiated species. Finally, removal of the lithio-directing and nitrogen-protecting dialkylaminomethyl functionality is readily achieved, with mild acid during the workup of the reaction, to give good yields of 1-substituted derivatives. The aminal method has also been used with 1,2,3,4-tetrahydrocarbazole, with lithiation being found to occur exclusively at the aromatic carbon to give the 8-lithio derivative **28**. This result contrasts with that seen with the related 2,3-dimethylindole, which underwent reaction solely on the 2-methyl group (88JOC794). The aminal derivative of benzo[*c*]carbazole gave a mixture of monolithio derivatives **29**, due to lithiation at both available sites, although reaction at the (naphtho) 6-position was favored. However, the dibenzo[*c,g*]carbazole aminal derivative, because of the symmetry of the molecule, gave cleanly the lithio derivative **30** as a result of reaction at the 6-position (88JOC794).



In further contrast to carbazole itself, benzo[*a*]carbazole readily undergoes direct lithiation without the need for a protecting group, with metalation occurring at the γ -position to give the 1,11-dilithio species (Scheme

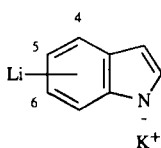
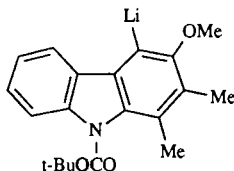
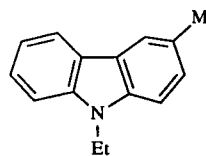


SCHEME 32

32), which then gives rise to good yields of 1-substituted derivatives after further reaction with suitable electrophiles (88JOC794, 88MRC347).

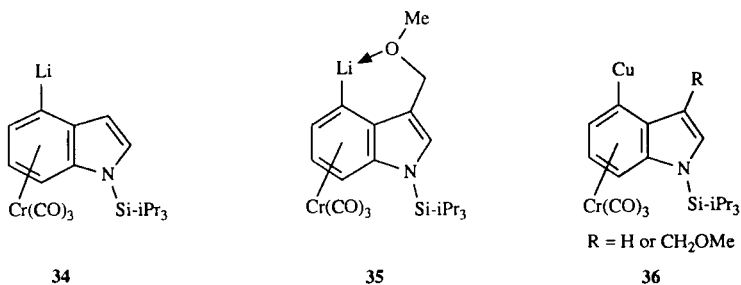
2. Nonadjacent to Nitrogen

Halogen-metal exchange reactions are the main route to fused-ring carbanions nonadjacent to nitrogen, and examples of metalated compounds formed by the use of exchange reactions include the 4-, 5- and 6-lithio derivatives of potassium indole **31** (86JOC5106) and the 4-lithiocarbazole derivative **32** [89JCS(P1)376], all of which are prepared from the analogous bromides by treatment with *t*-BuLi. Similarly, both the 3-lithium and the magnesium derivatives of 9-ethylcarbazole **33** can be prepared (36JOC146; 61JCS4921), whereas 3,6-dimetalated derivatives of carbazole have also been formed by double bromine-lithium exchange (41JA1553).

**31****32****33** M = Li or MgBr

The lithiation of tricarbonyl(η^6 -1-methyl-2-trimethylsilylindole)chromium(0) **26** to give mainly the 4-substituted derivative was mentioned above, but what was not mentioned was that if the *N*-methyl group is replaced by the bulkier triisopropylsilyl group then almost exclusive metalation at C-4 occurs to give **34**, even in the absence of a 2-substituent (82CC467). Small amounts of 5- and 6-substituted derivatives were also observed from this lithiation, but the extra chelation control conferred by a 3-methoxymethyl group allowed exclusive formation of the 4-lithio derivative **35** (88T7325). The range of electrophiles that would react with the 4-lithio derivatives **34** and **35** was found to be somewhat limited, but after transmetalation to the less basic copper complexes **36** a much wider range of electrophiles could be used. The resulting products could be

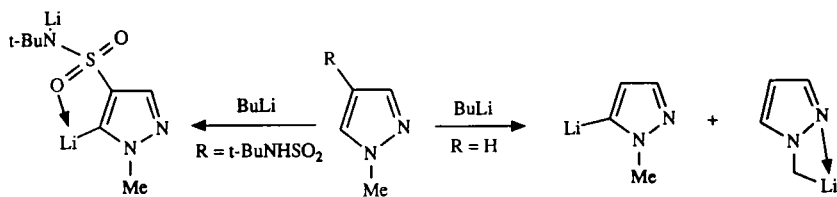
decomplexed ($h\nu/\text{air}$) and desilylated ($n\text{-Bu}_4\text{N}^+\text{F}^-$) in good yield to give a variety of 4-substituted indoles (88T7325).



C. PYRAZOLES AND INDAZOLES

1. Pyrazole 5-Carbanions

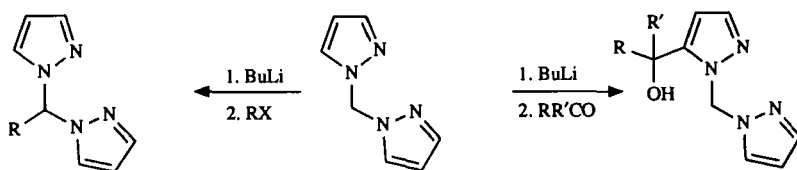
When protected with suitable N-substituents, pyrazoles undergo an α -metalation at the 5-position similar to that seen with pyrroles (Scheme 33)(79OR1; 88CHE117, 88KGS147). With 1-methylpyrazoles metalation



SCHEME 33

at the methyl group can also occur, but this external deprotonation, which is a result of kinetic factors, is not seen with higher alkyl groups (72JOC215; 83T2023). However, exclusive ring metalation, even in the presence of a 1-methyl group, can be achieved by the use of suitable 4-substituents, such as the *tert*-butylsulfonamido group, that direct metalation to the 5-position (91MI1).

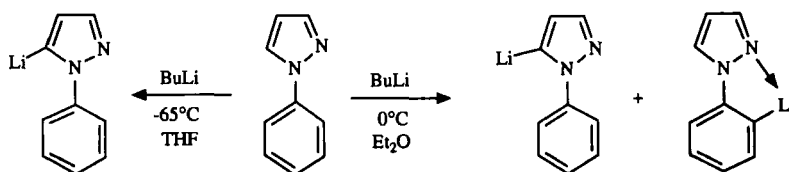
In some cases, the nature of the electrophile and the type of base used can determine the type of product isolated. For example, after treatment of bis(pyrazol-1-yl)methane (Scheme 34) with $n\text{-BuLi}$ at 25°C, reactive alkyl halides such as methyl iodide or benzyl chloride favor formation of the methylene substituted (kinetic) products, whereas with carbonyl



SCHEME 34

electrophiles under the same conditions, the ring substituted (thermodynamic) products are obtained (83T4133). In contrast, when LDA is used as the base, under reverse addition conditions at 0°C, 1-substituted products are formed exclusively, regardless of the nature of the electrophile employed (83T4133).

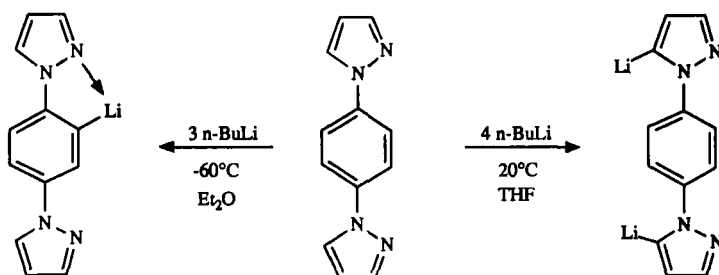
The lithiation of 1-phenylpyrazole in ether was also originally found to give mixtures of products (58JA6271), resulting from metalation at both C-5 and the ortho position of the phenyl ring (Scheme 35), but more recent



SCHEME 35

work has shown that by keeping the temperature below -65°C in THF, exclusive lithiation at C-5 can be achieved (85H943).

A similar difference in product distribution, between ether and THF as solvent, was seen with 1,4-di(1-pyrazolyl)benzene (80CB2740), but in this cast either exclusive benzene or pyrazole lithiation could be achieved, depending upon the reaction conditions (Scheme 36).



SCHEME 36

With pyrazoles it is possible in theory to use alkyl groups to protect the ionizable NH group (72JOC215) since they can subsequently be removed with pyridine hydrochloride (75JOC1353), but as yet this has not been put into practice. Removable protecting groups that have been investigated include benzyl (59LA55), tetrahydropyranyl (79OR1), *N*-pyrrolidinomethyl (88JOC5685), alkoxymethyl (89T4253), *tert*-butyldimethylsilyl [90JCS(P1)1829], phenylsulfonyl [90JCS(P1)1829], dimethylsulfamoyl (91CB1639, 91MI1) and 2-(trimethylsilyl)ethoxymethyl (SEM) [92H(34)303]. The *tert*-butyldimethylsilyl group was found to undergo migration to the carbanionic site and was therefore abandoned [90JCS(P1)1829], but 5-substituted derivatives have been successfully obtained with all of the other systems (Table III).

TABLE III
SYNTHESIS OF 3(5)-SUBSTITUTED PYRAZOLES VIA α -LITHIATION OF
N-PROTECTED DERIVATIVES

Entry	R	Metalation conditions	Yield (%)	Deprotection	Yield (%)	Reference
1	CH ₂ Ph	PhLi/Et ₂ O/20°C	57 ^a	Na/NH ₃	87	59LA55
2	THP ^b	<i>n</i> -BuLi/Et ₂ O/0°C	63–80	— ^c	— ^c	79OR1
3	CH ₂ NR ₂ ^d	<i>n</i> -BuLi/Et ₂ O/–78°C	— ^c	H ⁺ /Δ	45–78 ^f	88JOC5685
4	CH ₂ O [–] Li ⁺ ^g	<i>t</i> -BuLi/THF/–78°C	— ^c	H ⁺ ^h	51–76 ^f	89T4253
5	SO ₂ Ph ⁱ	PhLi/Et ₂ O/–78 → 0°C	8–65 ^j	OH [–] /MeOH	60–93	90JCS(P1)1829
6	SO ₂ C ₆ H ₄ Me	<i>t</i> -BuLi/THF/–78°C	55–100	— ^c	— ^c	92SL327
7	SO ₂ NMe ₂	<i>n</i> -BuLi/Et ₂ O/THF/–73°C	78 ^k	AcOH/Δ	77	91CB1639 ^l
8	SEM ^m	<i>n</i> -BuLi/THF/–70°C	29–46	<i>n</i> -Bu ₄ N ⁺ F [–]	60–63	92H(34)303

^a Yield for reaction with CO₂.

^b Starting material was 3-(4-chlorophenyl) derivative.

^c Deprotection not performed.

^d NR₂ = pyrrolidinyl.

^e Not isolated.

^f Overall reaction yield.

^g Formed *in situ*.

^h Either aqueous HCl or silica gel column used.

ⁱ Starting material was 4-bromo derivative.

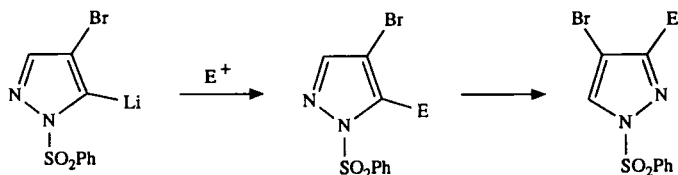
^j 8% yield is for reaction with PhCH₂Br where a complex mixture of products was obtained.

^k Yield for reaction with TMSCl.

^l See also 91MI1.

^m SEM = CH₂OCH₂CH₂SiMe₃.

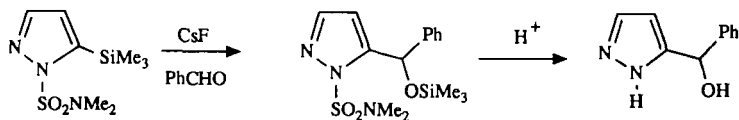
Lithiation of the benzyl derivative (entry 1) at -78°C occurs on the exocyclic methylene group (83T2023), but on warming to room temperature isomerization to the thermodynamically more stable 5-lithio isomer occurs. Experimental details concerning the lithiation of the tetrahydropyranyl derivative (entry 2) have not been published, although the lithiation step is reported to occur in 80% yield (79OR1). Hydrolysis is presumably quite facile. Product yields with the pyrrolidinomethyl derivative (entry 3) are lower than those for other amination protected heterocycles (88JOC5685), but since hydrolysis is performed during the workup of the reaction, they are still comparable with those from other routes to pyrazoles, which involve separate lithiation and hydrolysis steps. The alkoxymethyl derivative (entry 4) is formed *in situ* by reaction of a lithium base with 1-hydroxymethylpyrazole, which in turn can be prepared without isolation by reaction between pyrazole and formaldehyde (89T4253). After lithiation with a second equivalent of base, moderate to good product yields are obtained, with hydrolysis occurring on treatment with mild acid or elution through silica gel. The phenylsulfonyl group (entry 5) appears to be stable toward a variety of base systems, and lithiation occurs at the 5-position even in the presence of a 4-bromine atom. Thus α -lithiation occurred successfully when hard bases such as LDA and phenyl lithium were used [90JCS(P1)1829], although with softer bases such as *n*-BuLi less selectivity was seen, with some halogen-metal exchange also occurring. In some cases isomerization was observed, involving migration of the phenylsulfonyl group of the initial 1,4,5-trisubstituted product, to give the sterically less crowded 1,3,4-trisubstituted isomer (Scheme 37).



SCHEME 37

This rearrangement presents no problems, however, because, as with all of the other routes to pyrazoles, hydrolysis of the protecting group leads to a tautomeric mixture of the 3- and 5-substituted isomers. The dimethylsulfamoyl group (entry 7) represents a recent addition to the list of protecting groups for pyrazole, and in addition to having been used successfully in direct lithiation reactions (91CB1639, 91MI1), it has also

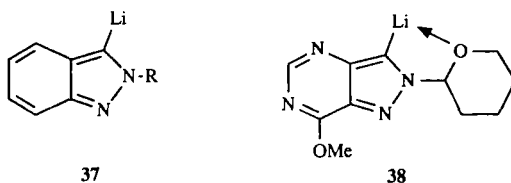
been used in conjunction with fluoride catalyzed desilylation in the presence of benzaldehyde (Scheme 38)(91CB1639).



SCHEME 38

Finally, the SEM derivative (entry 8) offers the advantage that the protecting group is stable to a variety of reaction conditions, although easily removed by fluoride ion, but unfortunately the reaction yields achieved in the lithiation step are not high [92H(34)303].

Bicyclic pyrazole derivatives display a similar reactivity to pyrazole itself; thus 2-substituted 2-*H*-indazoles undergo direct α -lithiation to give 3-lithio derivatives **37**(71JOU1601), whereas the tetrahydropyranyl (THP) derivative of 7-methoxypyrazolo[4,3-*d*]pyrimidine gave a similar species **38**, via halogen-metal exchange on the analogous bromide (79JOC505).



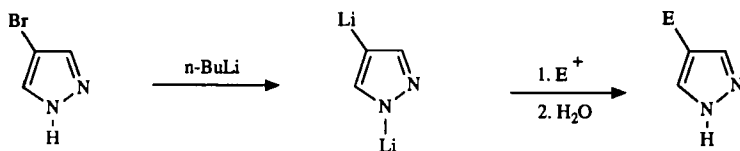
37

38

2. Pyrazole 4-Carbanions

The direct β -lithiation of a pyrazole derivative at the 4-position has recently been achieved (92CL357), although halogen-metal exchange reactions have more normally been performed. Thus both 4-bromo and 3,4,5-tribromopyrazole gave the analogous 4-acids on sequential treatment with 2 equivalents of *n*-BuLi and CO₂ (59LA55), whereas more recently a variety of other carbonyl electrophiles have been employed in this type of reaction (87API267; 91JHC1189). Although only moderate product yields are obtained, the convenient availability of the starting materials makes this a respectable route to 4-substituted pyrazole derivatives (Scheme 39).

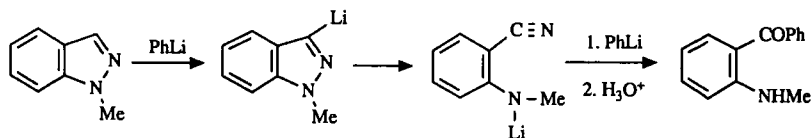
Better yields are obtained with N-substituted derivatives such as 1-methyl-4-bromopyrazole (59LA55), whereas 1,3-dialkyl-4-bromopyrazoles containing 5-chloro or 5-benzamido substituents also give good yields of 4-substituted derivatives after undergoing exchange with *n*-BuLi (71JOC2542; 84JHC1175).



SCHEME 39

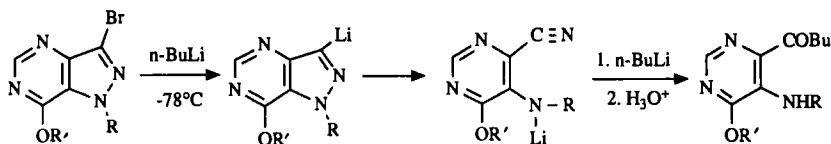
Less success has been obtained with removable N-substituents, however, the trityl and THP derivatives of 4-bromopyrazole both giving low yields of products derived from reaction of the lithio derivatives with carbonyl compounds [62CB222; 82ACS(B)101]. Magnesium metal has also been used to produce 1-methyl-4-(trimethylsilyl)pyrazole by an “*in situ* Grignard” reaction on the analogous 4-bromo compound in HMPT (84JOC4687).

β -Metalation and alkylation at the 3-position of N-substituted pyrazoles, which is also α -metalation with respect to the sp^2 -carbon, has not been successfully achieved, since by analogy with isoxazole and isothiazole (Section III,A), ring cleavage is to be expected. This situation is exemplified by 1-substituted indazoles, which undergo lithiation at the 3-position on heating with PhLi , with ring cleavage following on rapidly (Scheme 40) (74JOU2634, 74ZOR2617; 82KGS1078).



SCHEME 40

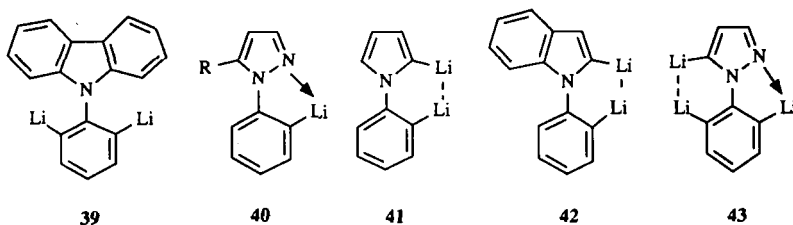
Generation of the 3-anion at low temperatures using halogen-metal exchange still fails to prevent ring cleavage, as was found with 1-substituted 3-bromopyrazolo[4,3-*d*]pyrimidines, which gave products of ring opening and subsequent butyllithium addition, even at -78°C (Scheme 41) (79JOC505).



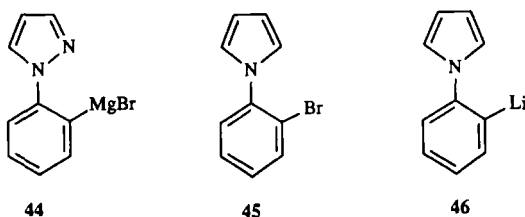
SCHEME 41

**D. PYRROLES, INDOLES, CARBAZOLES, AND PYRAZOLES:
LITHIATION IN AN N-PHENYL SUBSTITUENT**

N-Phenylcarbazole gives both a mono and a dilithio derivative **39**, although in low yield, as a result of metalation at the ortho positions of the phenyl ring (41JA1758; 43JA1729). Better yields are obtained with other systems where extra activation is available, and thus directed lithiation by the 2-aza atom of 5-substituted *N*-phenylpyrazoles results in good yields of products via the intermediacy of the lithio species **40** (70CJC2006; 85H943; 92CL357). Lithium atoms can also be used to direct lithiation, as is shown by the dilithiation of *N*-phenylpyrrole **41** [55JOC225; 79JOM(166)139] and *N*-phenylindole **42** (53JA375), as well as the trilithiation of *N*-phenylpyrazole **43** where both the 2-aza and 5-lithio atoms are able to act as lithiation directors (58JA6271).



Selective mono-metalation of the phenyl ring of unsubstituted *N*-phenylpyrroles and pyrazoles cannot be achieved with lithium reagents, because of their high basicity, although selectivity has been achieved in the pyrazole case using ethyl magnesium bromide to give **44** (74HCA1988). Selectivity can also be achieved by the use of halogen-metal exchange reactions, and thus *N*-(2-bromophenyl)pyrrole **45** is selectively lithiated at the 2'-position at -80°C to give **46** [81JOM(212)1], although at 0°C reaction is less specific, and the dilithio species **41** is formed [79JOM(166)139; 81JOM(212)1].



E. IMIDAZOLES AND BENZIMIDAZOLES

1. *Imidazole 2-Carbanions*

The metalation of imidazoles occurs at the 2-position adjacent to both heteroatoms (79OR1; 85H417; 88CHE117, 88KGS147), and the imidazole system actually represents one of the most studied of all nitrogen heterocyclic classes, when it comes to the α -metalation of protected derivatives with many different types of protection having been investigated. Removable groups that have been employed include benzyl (57JA4922; 66ACS2649), methoxymethyl (63JCS2195), benzenesulfonyl (77JHC517), ethoxymethyl [78JA3918; 83JA5337, 83JCS(P1)279], trityl (78JOC4381), dimethoxymethyl or diethoxymethyl (80JOC4038; 84JA2421), *N,N*-dimethylaminosulfonamido [84JCS(P1)481], [2-(trimethylsilyl)ethoxy]-methyl (SEM)(86JOC1891; 86TL4095; 88TL3411), 1-(1-ethoxyethyl) (88JOC1107), dimethylaminomethyl (88JOC5685), methoxyethoxymethyl (MEM), *t*-butoxymethyl, and benzyloxymethyl [90JCR(S)58](Table IV).

The relative merits of many of these protecting groups have been discussed previously [e.g., 84JCS(P1)481; 85H417; 88JOC1107, 88JOC5685], but as with the various pyrrole and indole protection systems it is sometimes difficult to make direct comparisons because of the nature of the different electrophiles employed by different research groups.

Benzylic N-protection (entry 1) is often unsatisfactory since competitive reaction at the exocyclic methylene can occur [84JCS(P1)481; 85S302]. As with bis(1-pyrazolyl)methane (Section II,C,1)(83T4133), the nature of the isolated product is determined by the type of electrophile used, with benzyl halides and, to a certain extent, iodomethane reacting at the *N*-benzyl carbon atom, whereas most other electrophiles give rise to the normal C-2 alkylated products (90JHC673). This result was interpreted in terms of steric rather than thermodynamic factors, since the two species that reacted at the benzylic carbon required a bulkier pentacoordinate transition state, whereas all of the others were able to react via a lower coordinate species (90JHC673).

Good lithiation yields can be achieved with alkoxymethyl derivatives (entry 2), due to their strong coordination ability, but severe deprotection conditions often lead to poor recovery of deprotected products. Low product yields are also often obtained with 1-benzenesulfonylimidazole (entry 3) (77JHC517), but this time the reason is due to a low nucleophilicity of the C-2 anion, caused by the electron-withdrawing nature of the substituent group.

1-Tritylimidazole (entry 4) lithiates readily in THF at room temperature, and it is interesting to compare this reactivity with that of the pyrrole

TABLE IV
SYNTHESIS OF 2-SUBSTITUTED IMIDAZOLES VIA α -LITHIATION OF
N-PROTECTED DERIVATIVES

Entry	R	Metalation conditions	Yield (%)	Deprotection	Yield (%)	Reference
1	CH ₂ Ph	<i>n</i> -BuLi/Et ₂ O/−50°C	68–81	Na/NH ₃	73 ^a	66ACS2649 ^b
2	CH ₂ OR ^c	<i>n</i> -BuLi/THF/−60°C	50–70	H ⁺ /Δ	42	78JA3918 ^d
3	SO ₂ Ph	<i>n</i> -BuLi/THF/0°C	7–18	OH [−] /EtOH	71 ^a	77JHC517
4	Ph ₃ C	<i>n</i> -BuLi/THF/0°C	35–98	HOAc/MeOH	73–99	78JOC4381
5	CH(OR ^c) ₂	<i>n</i> -BuLi/THF/−40°C	— ^e	H ⁺ /RT	36–84 ^f	80JOC4038 ^e
6	SO ₂ NMe ₂	<i>n</i> -BuLi/THF/−78°C	60–82	H ⁺ /Δ	100	84JCS(P1)481 ^h
7	SEM ⁱ	<i>n</i> -BuLi/THF/−78°C	20–100	H ⁺ or F [−]	46–100	86TL4095 ^j
8	CH(Me)OEt	<i>n</i> -BuLi/THF/−30°C	88–91	H ⁺ /55°C	88 ^a	88JOC1107
9	CH ₂ NMe ₂	<i>n</i> -BuLi/Et ₂ O/−70°C	— ^e	H ⁺ /RT	60–76 ^f	88JOC5685
10	CH ₂ OR ^k	<i>n</i> -BuLi/THF/−78°C	63–100 ^l	— ^m	— ^m	90JCR(S)58

^a Only one example given.

^b See also 57JA4922, 63JCS2195, 74JOC1374, 84JCS(P1)481, 85S302, and 90JHC673.

^c R = Me or Et.

^d See also 63JCS2195, 83JA5337, 83JCS(P1)279, 88TL5013, and 89JOC1439.

^e Not isolated.

^f Overall reaction yield.

^g See also 84JA2421 and 90S78.

^h See also 88TL5013 and 91CB1639.

ⁱ SEM = CH₂OCH₂CH₂SiMe₃.

^j See also 88TL3411.

^k R = CH₂CH₂OMe, *t*-Bu or CH₂Ph.

^l 100% value refers to yield of deuterated product. Best results were achieved with the benzyloxymethyl substituent (R = CH₂Ph).

^m Deprotection not attempted.

analog (Section, II,A) where α -lithiation failed to occur. The improved reactivity in the present case is a result of the activating effect of the second aza atom at C-3, which is also the reason that initial lithiation occurs at the 2-position, rather than at the 5-position, which is more "pyrrole-like." With the exception of halogenating agents, the lithiated trityl imidazole reacts with a variety of electrophiles in good yield (78JOC4381), although the method appears to be limited by the failure to form the initial *N*-trityl derivative with hindered imidazoles (80JOC4038).

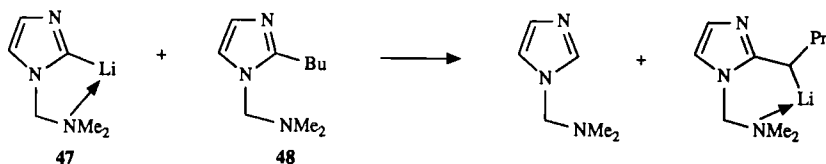
The dimethoxymethyl and diethoxymethyl derivatives (entry 5) lithiate readily at low temperatures in THF or ether and react in good yield with a range of electrophiles (80JOC4038; 90S78). As with the trityl group, hindered imidazoles cannot be protected with the larger diethoxymethyl group, although protection can still be achieved with the less bulky dimethoxymethyl group (80JOC4038). Hydrolysis under acid or neutral conditions occurs readily (83JA2382), but this has led other authors to criticize these groups as being too moisture sensitive (86JOC1891).

The dimethylsulfonamido derivative (entry 6) reacts with more reactive electrophiles in reasonable yields, although failure to react with weaker electrophiles such as DMF has been reported (88JOC1107), and thus it would appear that the electron-withdrawing effect of the sulfonamido group is similar to that seen with the benzenesulfonamide derivative (entry 3).

The SEM derivative of imidazole (entry 7) metalates much more easily than the analogous pyrrole, emphasizing once again the greater reactivity of the imidazole versus the pyrrole system. Reaction with some electrophiles proceeds in very good yield (86JOC1891, 86TL4095), although failure to react with a variety of alkylating and acylating agents has been reported (86TL4095). The relative expense of the SEM protection system versus alternative routes has also been noted (88JOC1107).

The 1-(1-ethoxyethyl) group (entry 8) overcomes the moisture sensitivity of the dialkoxymethyl protecting groups, yet still hydrolyzes with aqueous acid much more readily than the related methoxymethyl group (88JOC1107). Good yields of C-2 substituted products can be obtained, although the range of electrophiles investigated was small.

The dimethylaminomethyl group (entry 9) is easily introduced by a Mannich reaction, and lithiation occurs readily at -78°C (88JOC5685). After reaction with a variety of electrophiles, hydrolysis can be performed directly with aqueous acid to give 2-substituted imidazoles in good yield. However, the 2-lithio anion **47** was found to be quite basic, despite the base-weakening effect of coordination with the amino substituent, and thus it was capable of deprotonating the 2-butyl derivative **48** as it was formed by reaction with 1-bromobutane (Scheme 42). No such side-reac-



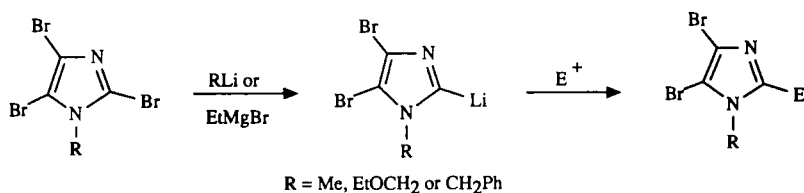
SCHEME 42

tion was observed with 1-iodobutane, presumably due to a faster rate of alkylation of the 2-lithio anion.

The above result has synthetic applications, and although beyond the scope of this review, the lithiation of dimethylaminomethyl-protected 2-methylimidazole has been used to produce products arising from exclusive metalation of the exocyclic methyl group (90TL5779).

In addition to the protecting groups discussed above, the methoxyethoxymethyl (MEM), *t*-butoxymethyl, and benzyloxymethyl groups (entry 10) have also been used to give successful C-2 lithiation [90JCR(S)58], with the best results being achieved with the benzyloxymethyl group. However, as yet no details on their ease of removal has been reported. Additional groups that have been unsuccessfully investigated include *tert*-butyl [84JCS(P1)481], a variety of acyl derivatives [84JCS(P1)481], and the lithium carboxylate [89MI3]. All of these systems were abandoned, either because of poor yields, inability to hydrolyze the protecting group, or too facile a cleavage under the conditions of the lithiation reaction.

In addition to direct metalation, halogen-metal exchange has also been used as a route to metalated imidazole derivatives (85H417; 88MI3), and with polyhalo derivatives the relative order of reactivity has been found to be the same as for deprotonation. Thus both 1-methyl and 1-ethoxymethyl-2,4,5-tribromoimidazoles were selectively monolithiated at C-2 with *n*-BuLi [81MI1; 83JCS(P1)735; 85H417], and a similar result was achieved with the benzyl derivative (Scheme 43), although in this latter case it was



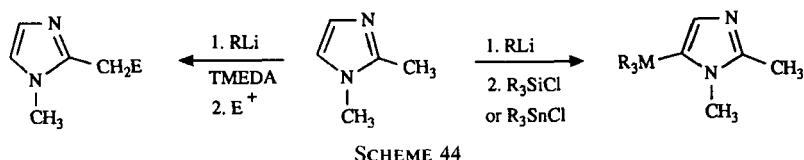
SCHEME 43

necessary to use bases such as EtMgBr, MeLi, *s*-BuLi, or PhLi in order to obtain selectivity, since reaction at either the 2- or 5-position was observed with *n*-BuLi [86TL1635; 87JCS(P1)1445, 87JCS(P1)1453; 88MI3].

Very good selectivity has also been achieved with iodinated imidazole derivatives, and thus the replacement of the 2-iodo group of 1-benzyloxymethyl-2,4,5-triiodoimidazole was achieved with *n*-BuLi in 99% yield (91JOC4296).

2. Imidazole 5-Carbanions

If the 2-position of an imidazole is blocked then α -lithiation can still occur, but this time at the 5-position, which has a reactivity similar to that of the pyrrole 2-position. A number of different blocking groups can be used at the 2-position, including ionizable groups such as SH (90S761), but with a 2-methyl group products arising from lithiation at both the C-5 and the exocyclic methyl groups are usually obtained [83JCS(P1)271; 85H417]. However, under certain conditions it is sometimes possible to obtain single products, arising from substitution either on the 2-methyl group or at the 5-position. Thus methyl substitution is favored under kinetic conditions, such as in the presence of TMEDA, whereas 5-substitution is favored with softer electrophiles such as trialkylchlorosilanes or stannanes (Scheme 44) [83JCS(P1)271].



The same protecting groups used in the C-2 lithiation of imidazoles can also be used for C-5 metalation when the 2-position is blocked. Thus the methoxy- and ethoxymethyl [78JA3918; 83JA5337, 83JCS(P1)279; 89JOC1439; 90JCS(P1)1645], dimethylsulfamoyl [86T2351; 90JCS(P1)1645; 91S1021], SEM (86JOC1891; 88TL3411), and 1-(1-ethoxyethyl) groups (88JOC1107), have all been reported to give rise to 5-metalation with 2-substituted imidazoles (Table V).

Removable groups employed to block the 2-position have included phenylthio [78JA3918; 83JCS(P1)279; 88TL3411], trimethyl and triethylsilyl (86T2351; 88TL3411), and *t*-butyldimethylsilyl [90JCS(P1)1645; 91S1021]. These blocking groups are usually added by an initial C-2 lithiation and reaction with the appropriate electrophile and can often be removed along with the nitrogen substituent as part of the workup of the reaction. Several steps can often be performed without isolation of intermediates; thus, 1-dimethylsulfamoylimidazole was converted to a 5-benzoyl-2-*tert*-butyldimethylsilyl derivative in 91% yield in a one-pot procedure (91S1021). Double deprotection was achieved in 99% yield to give the desired product (Scheme 45) (91S1021).

Halogen-metal exchange in conjunction with blocking the 2-position has also been used as a route to 5-substituted imidazoles; thus 2,4,5-

TABLE V
SYNTHESIS OF 4(5)-SUBSTITUTED IMIDAZOLES VIA α -LITHIATION OF N-PROTECTED
2-SUBSTITUTED DERIVATIVES

Entry	X	R	Metalation conditions ^a	Yield (%)	Reference
1	Ph	CH ₂ OEt	<i>n</i> -BuLi/THF/ -70°C	92 ^b	83JA5337 ^c
2		CH(Me)OEt	<i>s</i> -BuLi/THF/ -10 → 0°C	55–62	88JOC1107
3		CH ₂ OMe	<i>s</i> -BuLi/THF/ -40°C	59 ^d	89JOC1439
4		SEM ^e	<i>n</i> -BuLi/THF/ -78°C	54 ^d	92JOC2963
5	CH(OMe) ₂	CH(Me)OEt	<i>n</i> -BuLi/THF/ -40°C	78 ^d	88JOC1107
6	SPh	CH ₂ OR ^f	LDA/THF/ -60°C	38–70	78JA3918
7		CH ₂ OEt	<i>n</i> -BuLi/THF/ -70°C	61, 100	83JCS(P1)279 ^g
8		SEM ^e	<i>n</i> -BuLi/THF/ -78°C	79 ^h , 90 ^d	88TL3411
9	SiMe ₃	SEM ^e	<i>n</i> -BuLi/THF/ -78°C	83 ⁱ	88TL3411
10	SiEt ₃	SO ₂ NMe ₂	<i>s</i> -BuLi/THF/ -78°C	85–100 ^j	86T2351
11	SiMe ₂ t-Bu	CH ₂ OMe	<i>n</i> -BuLi/THF/ -78°C	90–100	90JCS(P1)1645
12		SO ₂ NMe ₂	<i>n</i> -BuLi/THF/ -78°C	66–100	90JCS(P1)1645 ^k

^a For deprotection conditions see individual references.

^b Yield for reaction with 0.33 mol diethyl carbonate.

^c See also 92JOC2963.

^d Yield for reaction with DMF.

^e SEM = CH₂OCH₂CH₂SiMe₃.

^f R = Me or Et.

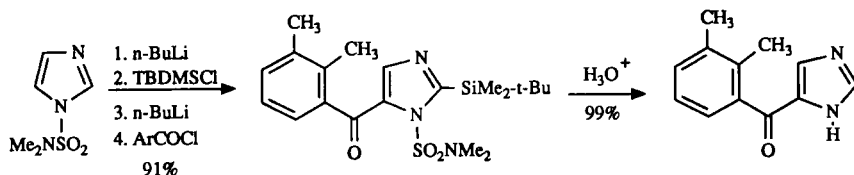
^g See also 81CC1095.

^h Yield for reaction with (TMSO)₂.

ⁱ Yield for reaction with Ph₂S₂ or DMF, includes hydrolysis of TMS group.

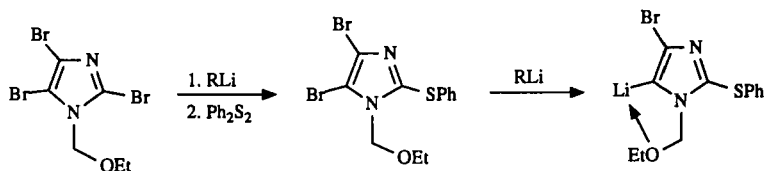
^j 100% yield is for deuteration.

^k See also 91SI021.



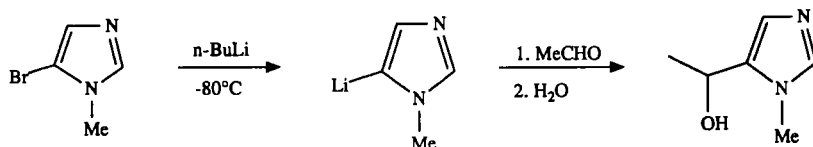
SCHEME 45

tribromo-1-ethoxymethylimidazole underwent selective bromine–lithium exchange at the 2-position, and after blocking of that position by a phenylthio group, further exchange occurred selectively at the 5-position (Scheme 46) [83JCS(P1)735].



SCHEME 46

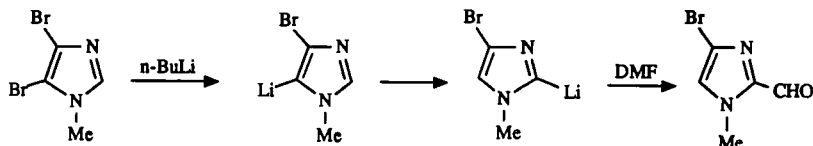
However, the real advantage of halogen-metal exchange is that metalation can now occur at the 5-position without the need to protect the 2-position. Thus the lithiation of 1-methyl-5-bromimidazole at -80°C gave the 5-lithio derivative, which was successfully reacted with acetaldehyde at that temperature (Scheme 47) (73JOC3762). The choice of halogen



SCHEME 47

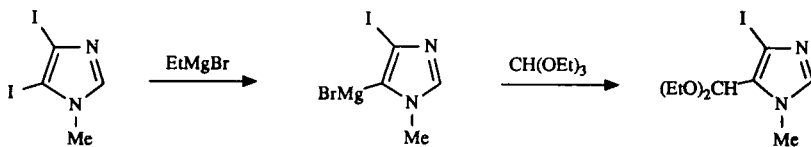
atom is important, however, because when the same type of reaction was performed with the analogous 5-chloro compound no exchange occurred, instead normal lithiation at C-2 was observed (73JOC3762).

Even after successful metalation at the 5-position of imidazoles, rearrangement to the more thermodynamically stable 2-lithio derivative can still occur, as was shown by the isolation of the 2-aldehyde product from the reaction of 1-methyl-4,5-dibromimidazole with *n*-butyllithium and DMF (Scheme 48) (81MI1).



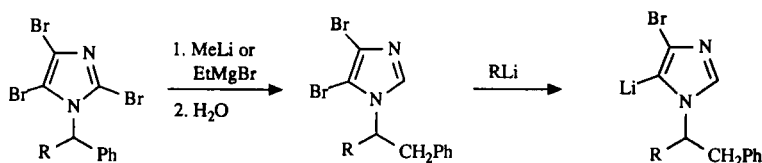
SCHEME 48

A similar type of transmetalation was also seen with 1,2-dimethyl-5-trimethylstannylimidazole, which gave the 5-lithio derivative at -100°C , but rearranged to the 2-lithiomethyl derivative at higher temperatures [83JCS(P1)271]. However, transmetalation does not occur with Grignard reagents and 5-substituted imidazoles can be successfully prepared via this route (Scheme 49) (81MI1; 82OPP409).



SCHEME 49

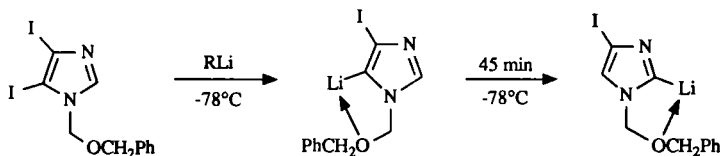
Halogen-metal exchange at the 5-position can also be used in conjunction with removable N-substituents, as was shown (Scheme 50) by



SCHEME 50

the lithiation of 1-benzyl-4,5-dibromoimidazoles, which were prepared from the analogous tribromo compounds by successive treatment with EtMgBr or 1 mol of MeLi and water [85CC1428; 87JCS(P1)1445; 88MI3].

1-Benzyloxymethyl-4,5-diiodoimidazole has also been selectively lithiated and derivatized at the 5-position (Scheme 51), although isomerization to

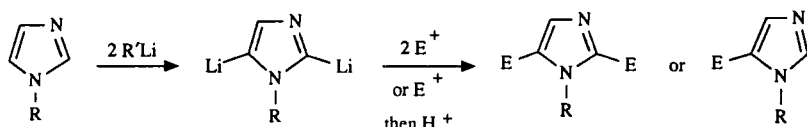


SCHEME 51

the analogous 2-lithio-4-iodo compound was found to be quite rapid, being virtually complete in 45 min at -78°C (91JOC4296).

3. Imidazole 2,5-Dicarbaniions

Under the appropriate conditions dilithiation at both the 2- and 5-positions of N-protected imidazoles can be achieved (Scheme 52), with 2,5-

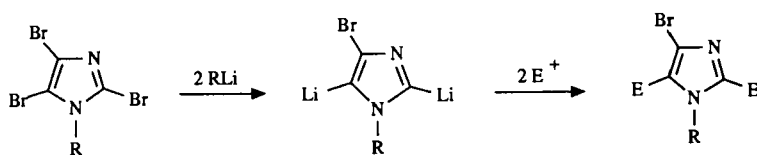


SCHEME 52

disubstituted products resulting from the addition of two or more equivalents of an electrophile [83JCR(S)196; 84JCS(P1)481; 90JCR(S)58]. Removable nitrogen protective groups that have been found best for this reaction are methoxymethyl and dimethylsulfonamido [84JCS(P1)481]. The greater reactivity of the 5-anion, compared to the 2-anion, was shown with the sulfonamido group, where addition of one equivalent of electrophile resulted in the formation of 5-monosubstituted derivatives as the major products [84JCS(P1)481].

Other groups that have been studied but found not to give quantitative dilithiation are trityl [84JCS(P1)481] and methoxyethoxymethyl (MEM) [90JCR(S)58]. The reason that dilithiation could not be completely achieved with the trityl derivative is reportedly because of a low solubility in diethyl ether, the solvent of choice for dilithiation work [84JCS(P1)481]. However, steric factors also play a part in this reaction as is shown by the fact that no dilithiation whatsoever was observed with the 1-(ethoxy)ethyl imidazole (88JOC1107), in sharp contrast to the situation seen with the less sterically hindered methoxymethyl analog [84JCS(P1)481].

Halogen-metal exchange can also be used as a route to dilithiated imidazoles, and 1-substituted 2,4,5-tribromoimidazoles have been selectively 2,5-dilithiated (Scheme 53) [81MI1; 85H417; 87JCS(P1)1453; 88MI3]. The benzyl group is the removable substituent most studied in this process [87JCS(P1)1453].



SCHEME 53

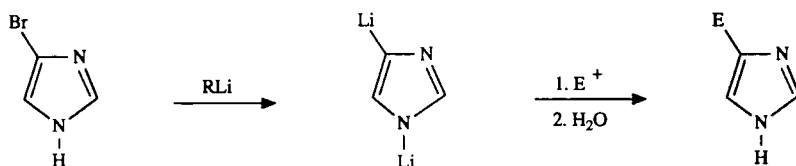
4. Imidazole 4-Carbanions

The metalation of imidazole in the 4-position, β - to the pyrrole-like nitrogen, but also α to the pyridine-like nitrogen, has received a lot of attention because of its difficulty compared to metalation at either the 2- or the 5-positions. This difficulty has been interpreted in terms of an *adjacent lone-pair* (ALP) effect whereby a ring-nitrogen atom bearing an sp^2 lone-pair provides a sizeable electrostatic obstacle to the generation of an sp^2 -carbanion at the adjacent ring-carbon atom (78JOC3565, 78JOC3570; 85JHC57). However, this effect is much smaller in a five-membered than in a six-membered ring. Indeed in a five-membered ring it

is probably activating, since imidazoles lithiate faster at the 2-position than at the 5-position. Nevertheless, there are few reports on the direct metalation of imidazoles at the 4-position; examples include the lithiation of 2-fluoro-1-tritylimidazole with *t*-BuLi (81EUP31708) and the metalation of 1-ethoxymethyl-5-methylthio-2-phenylthiomidazole with potassium diisopropylamide (KDA) [81CC1095; 83JCS(P1)279]. 2,4-dilithiation has also been reported in one case with the dimethylsulfamoyl derivative using *n*-BuLi in dimethoxyethane (91CB1639).

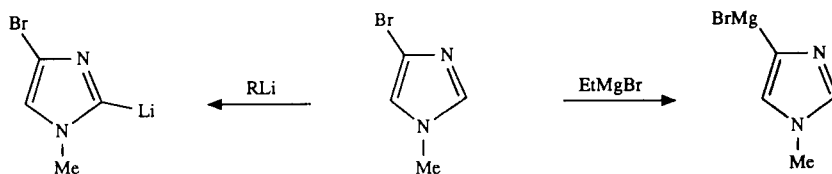
However, most approaches to overcoming the reluctance to carry a negative charge at C-4 have concentrated on halogen-metal exchange reactions, due to their lower activation energy requirement. Thus the lithiation of 4(5)-bromoimidazole has been achieved with 5 mol eq of *n*-BuLi (73ACS2179), or 2 mol eq of either lithium naphthalenide (82KGS1279) or *t*-BuLi [89JCS(P1)1139]. Moderate to good yields of products were obtained, depending on the electrophile used (Scheme 53).

4(5)-Bromoimidazole represents a special case in that ionization of the N—H group prevents deprotonation at C-2 or C-5, allowing replacement of the 4-bromine to occur (Scheme 54). The situation is quite different with



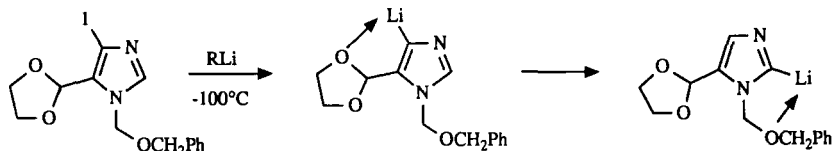
SCHEME 54

N-substituted derivatives, however, where deprotonation at the 2-position can occur in preference to halide replacement. Thus 4-bromo-1-methylimidazole undergoes lithiation at C-2 in preference to halogen-metal exchange at C-4 (73JOC3762), and only when the 2-position is blocked, as in the case of the 2-phenyl analog can reaction C-4 occur (83JA5337). Blocking groups are not necessary with weaker magnesium bases, however, and reaction at the C-4 position of 4-bromo-1-methylimidazole has successfully been achieved (Scheme 55) (81M11).



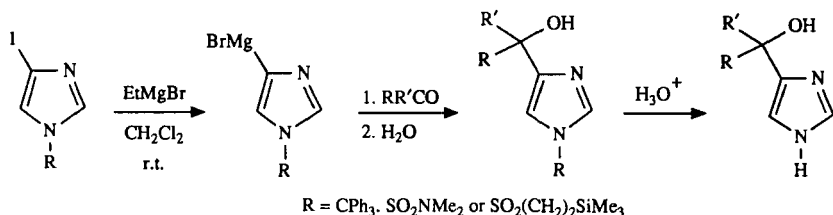
SCHEME 55

Alternatively, changing from bromide to the more reactive iodine can allow reaction to occur at C-4 with lithium bases. Thus halogen-metal exchange of the iodine atom in 4-iodo-1-tritylimidazole occurred readily, giving an 83% yield of the 4-aldehyde on reaction with DMF, although reaction with other electrophiles was not as successful (85JHC57). In addition to direct deprotonation at C-2, the 5-ethylene acetal protected 1-benzyloxymethyl derivative of 4-iodoimidazole also underwent some halogen-metal exchange with *n*-BuLi, but rapid rearrangement to the analogous 2-lithio derivative even at -100°C meant that 4-substituted derivatives could not be obtained (Scheme 56) (91JOC4296).



SCHEME 56

Rearrangement was also seen with the Grignard derivative of 1-(dimethylsulfamoyl)imidazole in THF, but interestingly no such rearrangement occurred when dichloromethane was used as the solvent at room temperature (91JOC5739). The trityl and [2-(trimethylsilyl)ethyl]sulfonyl derivatives also reacted efficiently under the same conditions, and a number of 4(5)-substituted imidazoles were able to be prepared in very good yield, after reaction of the magnesio compounds with a variety of aldehydes and ketones (Scheme 57) (91JOC5739). Reaction with a wider variety of

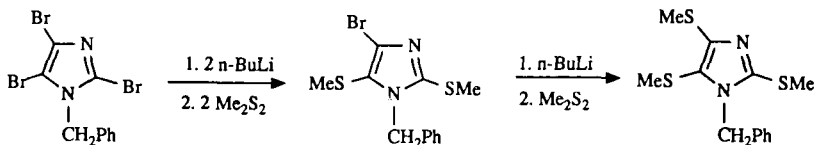


SCHEME 57

noncarbonyl electrophiles was also reported to be possible after transmetalation with zinc or copper salts (91JOC5739).

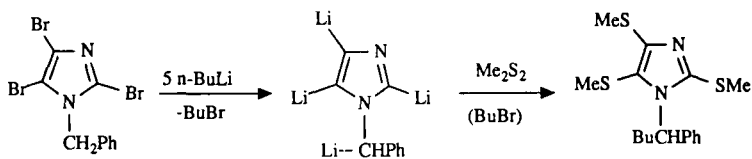
Halogen-metal exchange reactions on 2,4,5-tribromoimidazoles have shown that the 4-bromo atom is the most difficult to replace, with both the 2- and the 5-bromines able to be exchanged, either sequentially or in one step, without affecting the 4-position (88M13). Replacement of the 4-bromo

atom can then occur on further reaction of the 2,5-disubstituted derivative. An example of this occurs with the 1-benzyl derivative, where the 2- and 5-bromine atoms can be replaced by methylthio groups to give a species that is then capable of undergoing further reaction at the C-4 position (Scheme 58) [87JCS(P1)1453].



SCHEME 58

Interestingly, if the tribromo compound is treated with five equivalents of *n*-BuLi, then tetralithiation occurs, as was shown by the isolation of an α -butyl-2,4,5-trimethylthio derivative after reaction with excess dimethyldisulfide [87JCS(P1)1453]. The α -butyl group in the product is derived from reaction of the α -benzyl carbanion with the *n*-butyl bromide produced by the initial bromine–lithium exchange reaction (Scheme 59). However,



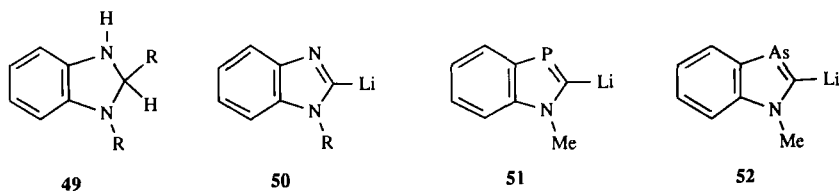
SCHEME 59

the exact course of the reaction is not clear, and alkylation of the side-chain carbanion may occur prior to halogen–metal exchange at C-4.

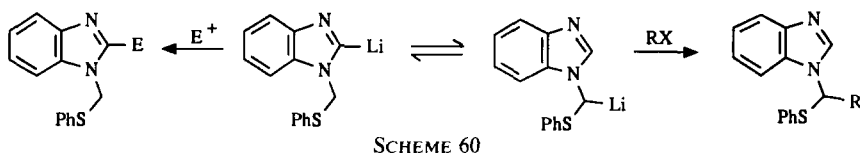
5. Benzimidazoles

The metalation of benzimidazoles at the 2-position is a slightly more complicated process than that for imidazoles, since nucleophilic addition to the azomethine double bond can occur under certain conditions to give 2,3-dihydro derivative **49** (58JOC1791; 88CHE117, 88KGS147). The added group can be either the initial base or a benzimidazole-2-anion derivative **50** formed *in situ* from a second equivalent of the starting material. The degree of addition versus C-2 deprotonation is greater for *N*-aryl benzimidazoles than for *N*-alkyl, but in either case addition can usually be avoided by the use of lower temperatures and the appropriate choice of base (88CHE117, 88KGS147). Replacement of the 3-aza atom in benzimidazole

by other group V elements does not appear to greatly affect the reactivity of the system, as the phosphorus and arsenic analogs similarly form the metalated derivatives **51** and **52** by reaction with lithium bases [83JOM(258)257].



The use of N-substituents that are capable of carrying a negative charge can lead to exocyclic metalation competing with that at C-2, thus whereas 1-(phenylthiomethyl)benzimidazole is initially lithiated at the 2-position, rearrangement to the exocyclic carbanion occurs at higher temperatures [87JCS(P1)775]. Reaction with most electrophiles can be achieved at C-2, but as with 1-benzylimidazole (Section II,D,1) and *gem*-bis(1-pyrazolyl)methane (Section II,C,1), benzyl bromide and certain alkyl halides react differently, giving products of reaction at the exocyclic methylene carbon (Scheme 60). Competitive metalation does not occur following oxidation



of the sulfur atom, and exclusive side-chain metalation is seen with both the sulfoxide and the sulfone analogs [87JCS(P1)775; 89MI3].

Removable N-protecting groups that have been investigated with the benzimidazole system include benzyl (74JOC1374), diethoxymethyl [82JCS(P1)2871], *N*-pyrrolidinomethyl (88JOC5685), vinyl (89TL1067), and lithioxymethyl (89JOC2949) (Table VI). Reference has been made to the use of other protecting groups such as dimethoxymethyl and trityl (89TL1067), but no details were given other than that reactions to give the 2-formyl derivatives were unsuccessful.

Clean metalation at C-2 is seen with the benzyl derivative (entry 1) (74JOC1374; 90JOC1399), despite the problems encountered with this protecting group in the imidazole system. The diethoxymethyl protected derivative (entry 2) also lithiates readily with *n*-BuLi in ether and gives good yields of deprotected derivatives [82JCS(P1)2871], although it has

TABLE VI
SYNTHESIS OF 2-SUBSTITUTED BENZIMIDAZOLES VIA α -LITHIATION OF
N-PROTECTED DERIVATIVES

Entry	R	Metalation conditions	Yield (%)	Deprotection	Yield (%)	Reference
1	CH ₂ Ph	<i>n</i> -BuLi/Et ₂ O/ -70°C → RT	25–40	H ₂ /Pd/C	65–70	74JOC1374 ^a
2	CH(OEt) ₂	<i>n</i> -BuLi/Et ₂ O/ -70 → -20°C	— ^b	H ⁺ /RT	4–83 ^c	82JCS(PI)2871
3	CH ₂ NR ₂ ^d	<i>n</i> -BuLi/Et ₂ O/ -78°C	— ^b	H ⁺ /RT	69–87 ^c	88JOC5685
4	CH ₂ O ⁻ Li ⁺ ^e	Rli/THF/ -20°C	— ^b	H ⁺ /RT	38–72 ^c	89JOC2949
5	CH = CH ₂	LDA/THF/ -78°C	87 ^c	O ₃ / -78°C	100	89TL1067

^a See also 90JOC1399.

^b Not isolated.

^c Overall reaction yield.

^d NR₂ = pyrrolidino.

^e Formed *in situ*.

^f LDA, *n*-BuLi, and *t*-BuLi all equally effective.

^g Yield for reaction with either DMF or EtOCHO to give the 2-aldehyde product.

been criticized because of its extreme moisture sensitivity (86JOC1891). The aminor and lithioxymethyl derivatives (entries 3 and 4) react in a manner similar to that of their imidazole or pyrazole analogs, whereas the vinyl derivative (entry 5) is reported to be superior to other groups when retention of the protective group is required during subsequent steps. The eventual removal of this group is achieved quantitatively by treatment with ozone in methanol (89TL1067).

6. Azabenzimidazoles

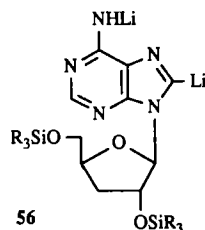
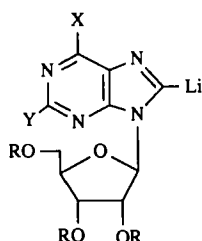
Other 1,3-diazaheterocycles related to the benzimidazole system that can be lithiated include purine nucleosides **53–55** and the related cordycepin analogs **56**, which undergo lithiation with LDA at the 8-position when the ribose or deoxyribose hydroxy groups, are suitably protected (87CPB72; 89JHC189). Some aspects of the nucleoside metalation work have been recently reviewed (89MII).

Aza-analogs of benzimidazole have also been successfully lithiated in combination with removable protecting groups, and thus the lithiated 1-SEM derivative of 7-azabenzimidazole **57** gave a 93% yield of the 2-

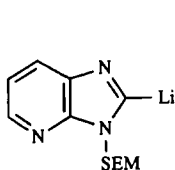
53 Adenosine: X = NH₂, Y = H

54 Guanosine: X = OH, Y = NH₂

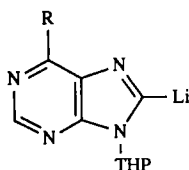
55 Inosine: X = OH, Y = H



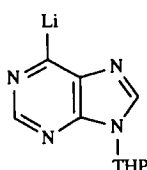
aldehyde after reaction with DMF (86JOC1891). Similarly a tetrahydropyranyl group was used to protect the *sp*³-nitrogen during the reaction of purine and 6-chloropurine with *n*-BuLi, with α -lithiation occurring at the 8-position to give **58** or **59**, respectively (79JOC4612). When the same reaction was performed on the THP derivative of 6-iodopurine at -100°C , halogen-metal exchange initially occurs to give the 6-lithio derivative **60**, but on warming to -78°C rearrangement to the thermodynamically more stable 8-lithio isomer **61** occurred. Either 6- or 8-substituted products can be obtained by this route depending upon the temperature at which the electrophile is added (79JOC4612).



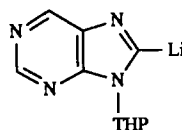
57



58 R = H; 59 R = Cl



60

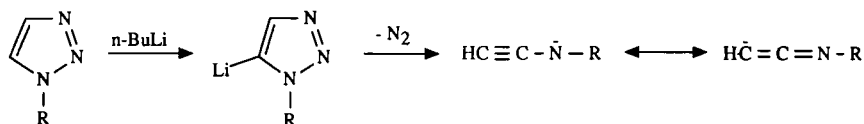


61

F. TRIAZOLES

1. 1-Substituted 1,2,3-Triazoles

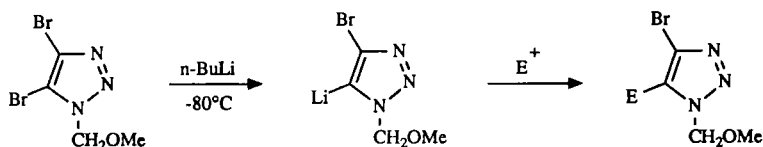
Of the four possible N-substituted triazole isomers, three contain a carbon atom adjacent to the pyrrole-like nitrogen, and all three undergo direct metalation at this position. Thus at temperatures below -20°C , 1-substituted 1,2,3-triazoles undergo successful lithiation and reaction with electrophiles at the 5-position (71CJC1792), but if the reaction temperature is allowed to rise to room temperature or above the metallated intermediates can undergo rapid fragmentation with loss of nitrogen (Scheme 61) [87AHC(41)41]. The ambident ketenimine anion formed by this fragmenta-



SCHEME 61

tion has been utilized synthetically by reaction with a variety of electrophiles [71CJC1792; 74LA1655; 91JCS(P1)775].

There do not appear to be any reports on the direct lithiation of 1-substituted 1,2,3-triazoles containing removable protecting groups, although preferential halogen-metal exchange with *n*-butyllithium at -80°C has been used to generate the 5-lithio derivative from 4,5-dibromo-1-methoxymethyl-1,2,3-triazole (Scheme 62) (88M13). The lithium com-

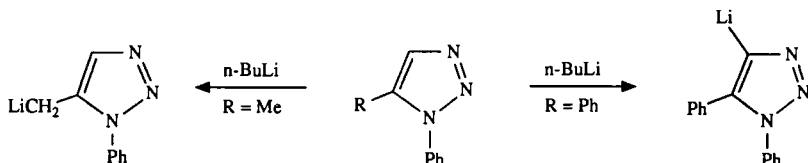


SCHEME 62

pound appears to be stable at low temperatures and (with the exception of aldehydes) produces products in moderate to good yield by reaction with a variety of electrophiles (88M13).

2. 1,5-Disubstituted 1,2,3-Triazoles

Because of the electron withdrawing effect of the extra nitrogen atom, the deprotonation of 1,5-disubstituted 1,2,3-triazoles at the 4-position is a more facile process than that for the related imidazoles, and the metalation of 1,5-diphenyl-1,2,3-triazole occurred readily, as was shown by the isolation of the 4-methyl derivative in 99% yield (71CJC1792). A different result was observed in the case of a 5-methyl group, however, where lateral metalation was found to be the preferred mode of reaction (Scheme 63) (71CJC1792).



SCHEME 63

3. 1-Substituted 1,2,4-Triazoles

1-Substituted 1,2,4-triazoles readily undergo α -lithiation at the 5-position, without any of the ring cleavage problems seen with the 1,2,3-isomers, and good yields of products can be obtained after reaction with electrophiles. Removable protecting groups investigated have included benzyl (74JOC940; 75LA1264; 86JHC1257), trityl (86JHC1257), pyrrolidinomethyl (aminal) (90T641), and [2-(trimethylsilyl)ethoxy]methyl (SEM) [92H(34)303] (Table VII).

Lithiation and substitution of the benzyl derivative (entries 1–3) at C-5 normally occur readily at -78°C ; however, as with the analogous imidazole, substitution at the exocyclic methylene occurs in preference when

TABLE VII
SYNTHESIS OF 3(5)-SUBSTITUTED 1,2,4-TRIAZOLES VIA α -LITHIATION OF
 N^1 -PROTECTED DERIVATIVES

Entry	R	Metalation conditions	Yield (%)	Deprotection	Yield (%)	Reference
1	CH_2Ph^a	$\text{PhLi}/\text{Et}_2\text{O}/-20^\circ\text{C} \rightarrow \text{RT}$	53 ^b	Na/NH_3	92	74JOC940
2		$n\text{-BuLi}/\text{THF}/-60^\circ\text{C}$	78–94	Na/NH_3	90–99 ^c	75LA1264 ^d
3	CH_2Ph^e	$n\text{-BuLi}/\text{THF}/-78^\circ\text{C}$	50–95 ^f	Na/NH_3	80 ^g	86JHC1257
4	CPh_3	$n\text{-BuLi}/\text{THF}/-78^\circ\text{C}$	61, 95 ^h	— ^j	— ⁱ	86JHC1257
5	CH_2NR_2^j	$n\text{-BuLi}/\text{THF}/-78^\circ\text{C}$	54–95 ^k	$\text{NaBH}_4/\text{EtOH}$	89–98	90T633
6	SEM ^l	$n\text{-BuLi}/\text{THF}/-70^\circ\text{C}$	30–57	$n\text{-Bu}_4\text{N}^+\text{F}^-$	90 ^g	92H(34)303

^a Starting material was 3-phenyl derivative.

^b Yield for reaction with benzophenone.

^c A 52% yield was obtained in one example with deprotection using $\text{H}_2/\text{PD/C}$.

^d See also 85S302, 86JHC1257.

^e Starting material unsubstituted at 3-position.

^f 95% value represents isolated yield of material with greater than 90% deuteration.

^g Only one example given.

^h Yields for reaction with benzophenone and CD_3OD (over 90% deuteration); reaction with other electrophiles was unsuccessful.

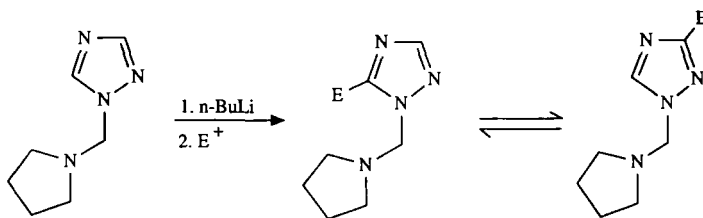
ⁱ Deprotection not attempted.

^j NR_2 = pyrrolidino.

^k Spontaneous deprotection observed in some cases.

^l SEM = $\text{CH}_2\text{OCH}_2\text{CH}_2\text{SiMe}_3$.

benzyl chloride is used as the electrophile (85S302; 90JHC673). Where stability of the 5-substituent permits, removal of the benzyl protecting group can be achieved with sodium in liquid ammonia. The trityl derivative (entry 4) lithiates successfully at -78°C , but its reaction with electrophiles is apparently restricted due to steric factors (86JHC1257). The aminor derivative (entry 5) also lithiates with *n*-BuLi at -78°C , but after reaction with various electrophiles the initially formed 5-substituted product can undergo isomerization to produce an equilibrium mixture that consists mainly of the less sterically hindered 3-substituted compound (Scheme 64) (90T641).



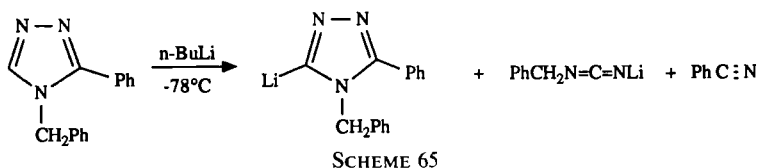
SCHEME 64

This isomerization was confirmed by means of a detailed kinetic NMR study (90T633), but is not detrimental to the synthesis of substituted 1,2,4-triazoles, because in all cases removal of the protecting group leads to a tautomeric mixture of 3- and 5-substituted products. The methods available for removal of the aminor function actually depend upon the nature of the added C-5 substituent, with acid hydrolysis occurring only in some cases. More commonly, treatment with NaBH_4 in refluxing ethanol is the method of choice (90T633). Lithiation and derivatization of the SEM protected compound (entry 6) can be achieved without the isomerization shown by the aminor derivative, and deprotection can be achieved with either aqueous acid or anhydrous fluoride ion [92H(34)303]. However, overall reaction yields are not as high as those for the aminor system.

4. 4-Substituted 1,2,4-Triazoles

4-Substituted 1,2,4-triazoles have received less attention than their isomeric counterparts, but those results that are available indicate that their lithio derivatives are less stable than their 1-substituted isomers. Thus, in addition to undergoing the expected α -lithiation and reaction at the 5-position, 3-phenyl-4-benzyl-1,2,4-triazole also gave products resulting from ring-opening, even at -78°C (Scheme 65) (86JHC1257).

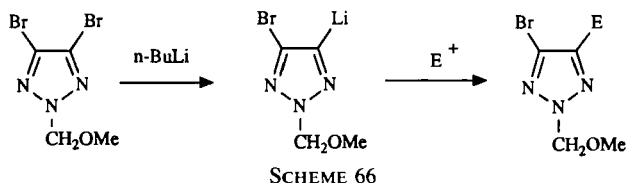
Apart from the above benzyl derivative no other removable substituent



has been investigated, but that is not so important, since removal of the 4-substituent gives rise to the same tautomeric mixture as is obtained from the 1-substituted isomers.

5. 2-Substituted 1,2,3-Triazoles

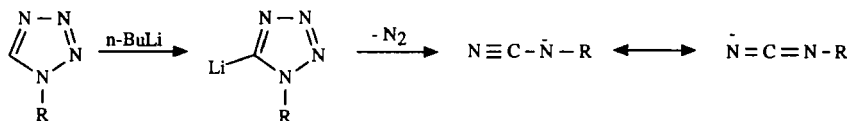
The direct metalation of a 2-substituted 1,2,3-triazole at the 4-position has not been reported, although halogen-metal exchange has been used to achieve this result. Thus the symmetrical 4,5-dibromo-2-methoxymethyl-1,2,3-triazole undergoes a single bromine-lithium exchange to generate the 4-bromo-5-lithio derivative, which can be reacted with electrophiles at -80°C (Scheme 66) (88MI3).



G. TETRAZOLES

1. 1-Substituted Tetrazoles

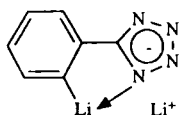
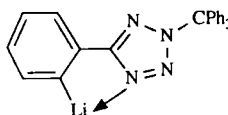
1-Substituted tetrazoles undergo metalation at C-5, but the resulting lithio species appear to be considerably more prone to ring opening than the analogous triazoles (67JOC3580; 71CJC2139). Thus 1-phenyltetrazole undergoes immediate decomposition with loss of nitrogen on reaction with *n*-butyllithium at -70°C , and the related 1-methyl analog undergoes a similar breakdown at temperatures above -50°C (Scheme 67), although



this latter compound is sufficiently stable below -60°C that it can be successfully reacted with a variety of electrophiles at low temperatures (71CJC2139).

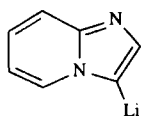
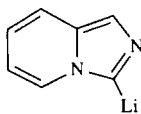
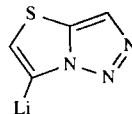
2. 5-Phenyltetrazoles in the Phenyl Ring

Recently the tetrazole moiety has attracted interest as a useful directing group for the lithiation of 5-aryl substituents, with the dianion derivative **62** being obtained in the case of the unsubstituted parent compound and the monolithio species **63** in the case of the 2-trityl derivative (91TL6857; 91USP5039814). With both systems, good yields of products were obtained after reaction with a variety of electrophiles.

**62****63**

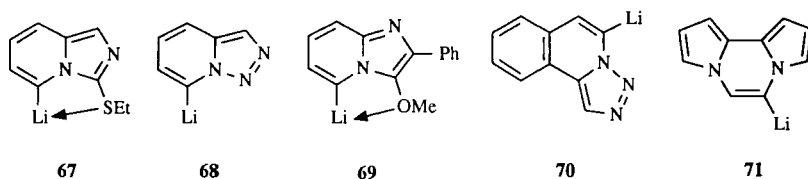
H. AZAINDOLIZINES AND OTHER BRIDGEHEAD NITROGEN HETEROCYCLES

There are several examples of bicyclic and tricyclic heterocycles containing bridgehead nitrogen atoms that undergo α -metalation with respect to that atom. Thus, both imidazo[1,2-*a*] and imidazo[1,5-*a*] pyridine undergo direct metalation in the 5-membered ring, adjacent to the *sp*³-nitrogen, to give the 3-lithio derivatives **64** and **65** (68JOC1638; 72JHC1157). Similarly, 1,2,3-triazolo[5,1-*b*]thiazole preferentially gives the 6-lithio derivative **66**, although some reaction at the C-3 position in the triazole ring does also occur (91T2861). However, if the 3-position is substituted, then exclusive 6-lithiation occurs.

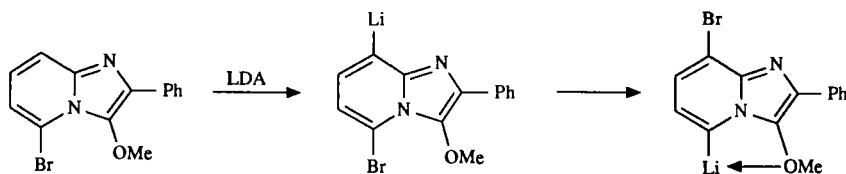
**64****65****66**

Metalation can also occur adjacent to the bridgehead *sp*³-nitrogen in six-membered rings, and examples include the lithio derivatives of 3-ethylthioimidazo[1,5-*a*]pyridine **67** (80TL2195, 80TL4193), 1,2,3-triaz-

olo[1,5-*a*]pyridine **68** [80TL4529; 82JCS(P1)967], 3-methoxy-2-phenylimidazo[1,2-*a*]pyridine **69** (83S987), 1,2,3-triazolo[5,1-*a*]isoquinoline **70** [84JCR(M)1430; 84JCR(S)140; 85JCS(P1)1897], and dipyrrolo[1,2-*a*:2', 1'-*c*]pyrazine **71** (91H85).



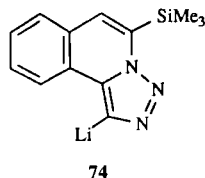
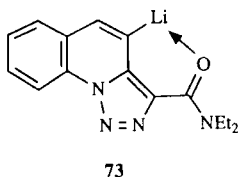
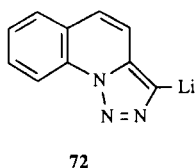
The synthetic utility of the second example is enhanced by the fact that cleavage to 6-substituted pyridine-2-aldehydes can be achieved in a two-step bromination–hydrolysis sequence [82JCS(P1)967]. The methoxy group in the third example serves not only to block the normally metalated 3-position, but also to direct lithiation to the 5-position. This directing effect is confirmed by contrast with a nondirecting methyl group at C-3, where mixtures of 5- and 8-substituted products were obtained (83S987). The stabilizing effect of the 3-methoxy group was further confirmed when, after initial β -lithiation of the analogous 5-bromo compound, migration of the bromine atom via a “halogen dance” mechanism resulted in formation of the thermodynamically more stable 5-lithio-8-bromo derivative (Scheme 68) (83S987).



SCHEME 68

β -Metalation also occurs in other systems that lack α -protons capable of being removed, and thus 1,2,3-triazolo[1,5-*a*]quinoline gave the lithio derivative **72**, resulting from lithiation in the 5-membered ring [84JCR(M)1430, 84JCR(S)140]. However, lithiation in the 6-membered ring could also be achieved, provided that the normally lithiated 2-position carried a group capable of directing metalation [84JCR(M)1430, 84JCR(S)140]. An example is the *N,N*-diethylcarboxamide **73**. With 1,2,3-triazolo[5,1-*a*]isoquinoline, α -lithiation normally occurs in the 6-membered ring, but if that position is blocked, for example, by a trimethylsilyl group, then it is possible to obtain the β -lithio derivative **74**, where met-

alation has occurred at the 1-position in the 5-membered ring [87JCS(P1)1865].

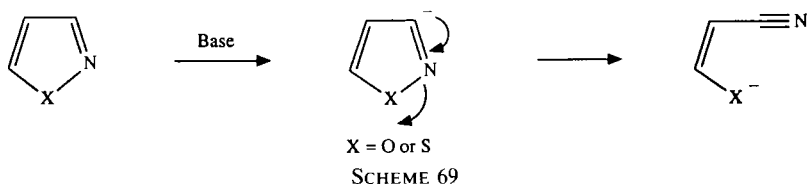


III. Ring sp^2 -Carbanions of Azoles Containing O and/or S

The oxa and thia 2- and 3-heteroazoles are isoelectronic with N-substituted pyrazoles and imidazoles, which were discussed in Section II,C, but although there are many similarities there are also some significant differences, the most notable of which is the propensity for ring-opening reactions to occur under basic conditions [87AHC(41)41].

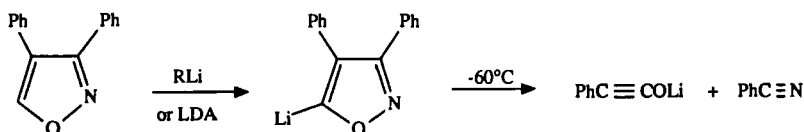
A. ISOXAZOLES AND ISOTHAZOLES

Although examples of the cleavage of pyrazoles and indazoles are rare, the same cannot be said of the related isoxazole and isothiazole systems where cleavage is often quite facile with deprotonation at C-3 being the favored mode of reaction (Scheme 69) [87AHC(41)41].



1. Isoxazoles

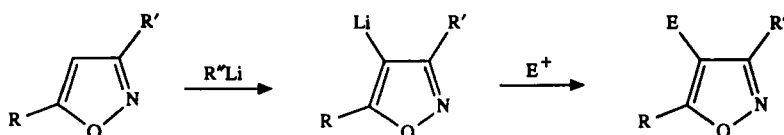
Isoxazoles and benzisoxazoles that are unsubstituted at the 3-position readily undergo the base-reduced ring fragmentation shown above, and there are therefore no reports on the successful metalation of these types of compound. 3-substituted isoxazoles do undergo lithiation, at the 5-position, but ring fragmentation rapidly follows, even at -60°C in the case



SCHEME 70

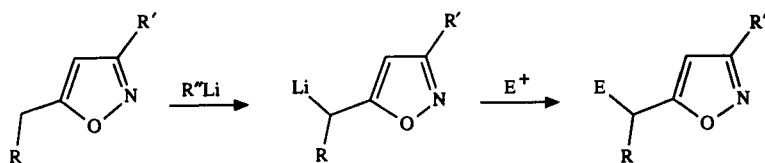
of the 3,4-diphenyl derivative (Scheme 70) [75AG(E)765; 79LA219]. This cleavage reaction has been used synthetically to produce β -lactones, trimethylsilylketenes, and azetidinones [75AG(E)765; 79LA219; 81CC404].

When both the 3- and the 5-positions of isoxazole are substituted, stable metalated derivatives can be obtained via direct lithiation at C-4, with subsequent reaction giving rise to a variety of 3,4,5-trisubstituted in very good yields (Scheme 71) (70CJC1371).



SCHEME 71

However, the results obtained are highly dependent on the nature of the substituents, and when the 5-substituent is a methyl, alkoxymethyl, or alkylthiomethyl group, side-chain metalation becomes the predominant reaction type (Scheme 72) [68JCS(C)172; 70CJC2006; 76JCS(P1)994;

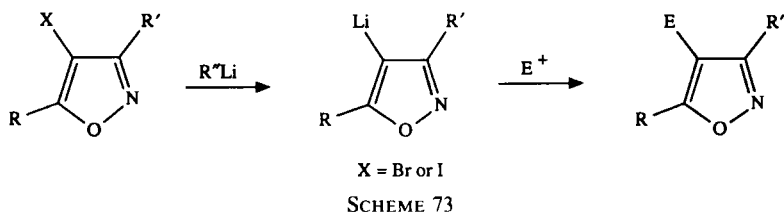


$\text{R} = \text{H}, \text{O-alkyl or S-alkyl}$

SCHEME 72

85H585]. Lateral metalation actually becomes the exclusive mode of reaction when LDA is used as the base [76JCS(P1)994; 83JOC4307].

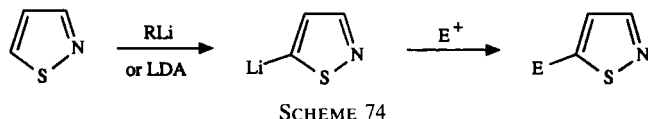
The degree of 4-lithiation with $n\text{-BuLi}$ can be increased by the presence of 3-substituents that favor ortho lithiation [68JCS(C)172; 76JCS(P1)994], but in no case has exclusive 4-metalation been seen. However, clean metalation at C-4, even in the presence of C-5 alkyl substituents, can be achieved by the use of halogen-metal exchange reactions (Scheme 73), and both bromo and iodo derivatives have successfully been used for



this transformation [75HC49; 80JOM(195)275; 84JMC1245; 89H(29)667; 91H1757].

2. Isothiazoles

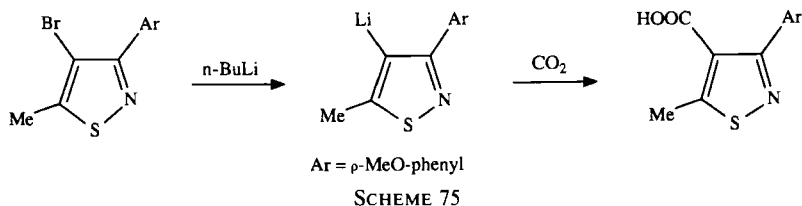
In a manner analogous to that seen with N-substituted pyrazoles (Section II,D), isothiazole undergoes lithiation at the 5-position, adjacent to the sp^3 -heteroatom, and reaction with electrophiles then leads to a variety of 5-substituted derivatives (Scheme 74) [64JCS446; 72AHC(14)1; 84JMC1245].



Metalation occurs readily at -70°C , and successful reaction has even been achieved in the presence of 4-bromo or 4-carboxylic acid groups (64JCS446; 68CPB148), although some halogen-metal exchange was also observed in the former case (68CPB148). A small amount of ring-cleavage product, presumably derived from deprotonation at C-3, was observed with 4-methylisothiazole (70CJC2006), but when that position is blocked, as with 3-methylisothiazole, a different mode of cleavage is seen, with nucleophilic attack of the base on the sulfur atom apparently being favored (64JCS446; 70CJC2006). Presumably because of these ring-cleavage reactions, low yields have often been reported when using *n*-BuLi as the base [e.g., 68JCS(C)611; 75JHC49; 84JMC1245], but more recently LDA has been found to be a much superior reagent for this system, with good to excellent yields achieved in condensations with carbonyl compounds (88CJC1617).

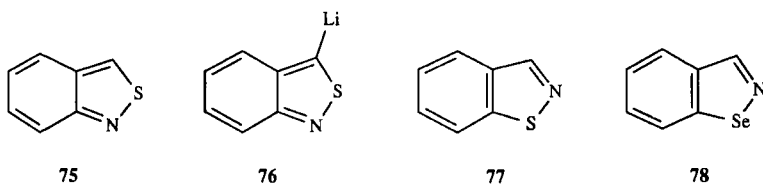
Halogen-metal exchange has also been used to give a 5-lithioisothiazole derivative (73JMC978), but this route appears to offer no advantage over direct metalation. However, direct metalation of 3,5-disubstituted isothiazoles at the 4-position has not been reported, and in this case halo-

gen-metal exchange would appear to be the preferred route, with the lithiation and carboxylation of a 4-bromoisoxazole derivative having been reported (Scheme 75) (68CPB148), although no yield was given.



3. Benzisothiazoles

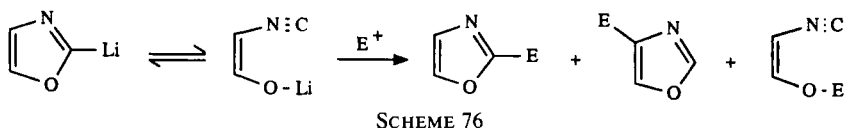
2,1-Benzisothiazole **75** undergoes direct metalation at C-3, adjacent to the sulfur atom, to give the lithio derivative **76** (75JHC877), but there are no reports on the lithiation of the isomeric 1,2-benzisothiazole **77**. The related 1,2-benzisoselenazole **78** does undergo lithiation at C-3, but this is followed by cleavage analogous to that seen with 1,2-benzisoxazole (75JHC1091), and it is to be assumed that 1,2-benzisothiazole would undergo a similar fate.



B. OXAZOLES

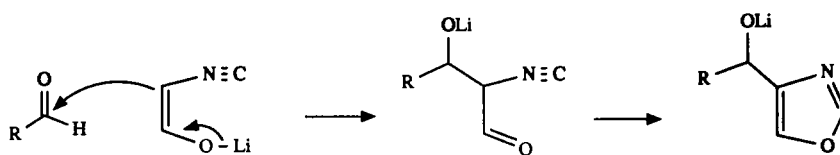
1. Oxazole 2-Carbanions

Oxazoles undergo lithiation at the C-2 position, although the lithiated heterocycle is in equilibrium with a ring-opened form, and depending on the nature of the electrophile, either cyclic or acyclic derivatives can be obtained (Scheme 76) (75LA533; 80JOC2548; 84S1048; 87JOC3413,



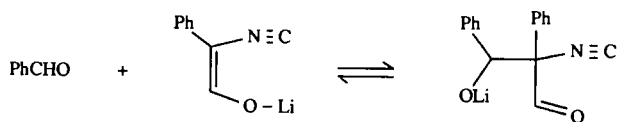
87S693; 91JOC3058), but in this case, in addition to the expected 2-substituted oxazoles, 4-substituted derivatives can also be obtained (91JOC449).

The anomalous 4-substituted derivatives are observed only when aldehydes are employed as the electrophiles, but interestingly they are almost exclusively the sole products formed in this case. Their formation is believed to arise via reaction with the lithium enolate form of the ring-opened species, with subsequent enolization and ring closure giving rise to the observed products (Scheme 77)(91JOC449).



SCHEME 77

With 4-substituted oxazoles, normal reaction at C-2 is observed with aldehydes (80JOC2548), although the yields obtained were found to be very time dependent (91JOC3058). When benzaldehyde was reacted with the anion of 4-phenyloxazole, the product yield was significantly improved by allowing more time between the addition of the aldehyde and the aqueous acid quench. This result was interpreted as being due to reversible reaction between the aldehyde and the ring-opened form of the oxazole (Scheme 78)(91JOC3058), and although two possible adducts were origi-



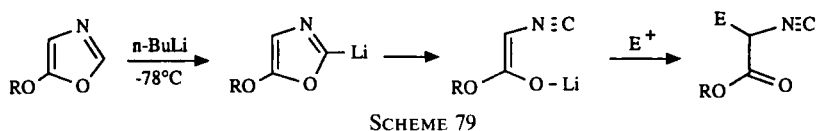
SCHEME 78

nally proposed, the correct one is almost certainly the one that is derived by alkylation of the enolate, since this route is entirely analogous to that proposed above to account for the formation of 4-substituted oxazoles (91JOC449).

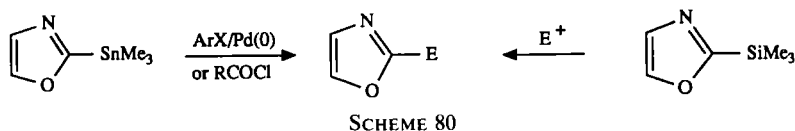
Because of the presence of the extra phenyl substituent in the present case, further enolization is prevented, and therefore ring closure to an oxazole cannot occur. Thus, prevented from further reaction, the adduct undergoes a slow breakdown to reproduce the original enolate, and the 2-oxazole anion, which is then able to react irreversibly with the benzaldehyde to produce the observed 2-substituted oxazole product.

Another exception to the normal mode of reactivity is seen to occur

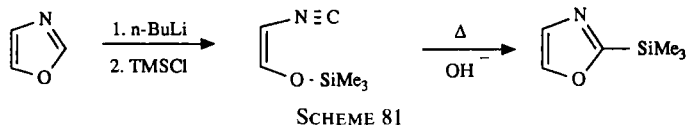
with 5-alkoxyoxazoles (79JOC2042), where the alkoxy group appears to stabilize the ring-opened form to such an extent that no oxazole products are observed, even with electrophiles, such as D_2O , which normally give good yields of ring-closed products. That the isolated products are derived by alkylation of the enolate form (Scheme 79) is further support for the reaction pathways proposed above.



To overcome some of the problems associated with the synthesis of 2-substituted oxazoles via lithiation reactions, a number of alternative methods have been investigated. Thus 2-trimethylstannyloxazoles have been used in both palladium cross-coupling reactions and direct reaction with acid chlorides (87S693; 88G211), whereas 2-trimethylsilyl derivatives have been used in direct reactions with acid chlorides, aldehydes, ketenes, and azolium salts (Scheme 80)(84CC258; 87JOC3413; 88G211).



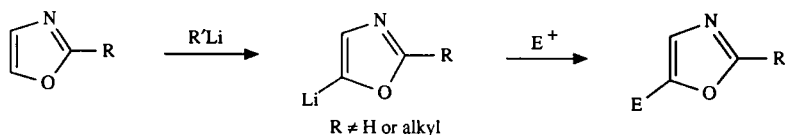
The trialkylstannyl derivatives are obtained directly by reaction of trimethyltin chloride with 2-lithiooxazole (87S693), but in the case of the silyl compounds an extra step is required, involving the base-catalyzed thermal ring closure of the silylated ring-opened oxazole (Scheme 81)(84CC258; 87JOC3413).



Unfortunately the silyl ring-closure reaction does not appear to be a general phenomenon, and although successful reaction has been reported with the 4-methyl and 5-phenyl derivatives (84CC258; 87JOC3413), the same was not true of the analogous 4-phenyl and 5-(2-thienyl) derivatives (87JOC3413; 91JOC3058).

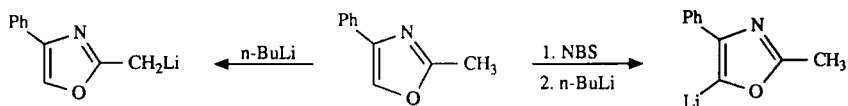
2. Oxazole 5-Carbanions

If the 2-position of oxazole is substituted by a group other than an alkyl group, then lithiation occurs at the 5-position (Scheme 82)(84JOC4325; 91JOC3058).



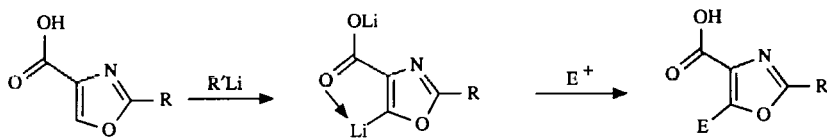
SCHEME 82

In the case of 2-alkyl derivatives, deprotonation occurs preferentially at the substituent α -position (91JOC3058), although in some cases this problem can be overcome by the use of consecutive bromination and halogen-metal exchange reactions, as was shown with 2-methyl-4-phenyloxazole (Scheme 83)(68OMS13).



SCHEME 83

However, it is still possible to achieve metalation at the 5-position, even in the presence of a 2-alkyl group, and more interestingly even in the absence of a 2-substituent, provided that a strong lithiation directing group is situated at the 4-position. Thus, both oxazole-4-carboxylic acid and its 2-methyl derivative undergo directed lithiation at C-5, despite the presence of acidic C-2 or methyl protons (Scheme 84)(81TL3163; 86JOC5111). In



SCHEME 84

fact, only after blocking of the 5-position with a trimethylsilyl group was it possible to achieve alkylation of the methyl group (83TL4391).

Halogen-metal exchange has also been used to produce 2-aryl-5-substi-

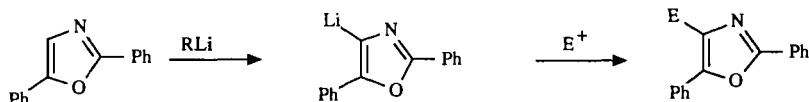
tuted oxazoles (Scheme 85), not because of any problems with the direct lithiation, but because of the greater availability of the starting materials (89S873).



SCHEME 85

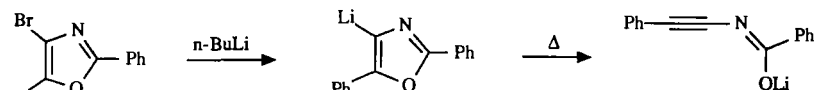
3. Oxazole 4-Carbanions

The least acidic of the three available position on oxazole is the 4-position, but even this can be lithiated under the appropriate conditions (86CRV845). Thus, while 2,5-diphenyloxazole gives a mixture of products on treatment with *n*-BuLi, clean metalation at C-4 can be achieved using LDA or KDA (86CRV845), or with *s*-BuLi and a catalytic amount of LiTMP (Scheme 86)(91JOC3058).



SCHEME 86

Formation of the same 4-lithiooxazole had previously been achieved using halogen-metal exchange with the analogous bromide [68T3965; 76JCS(P1)989], and this reaction was used to show that 4-lithiooxazoles are much more stable species than the analogous 2-lithio derivatives, with ring cleavage only being seen on heating the lithiated oxazole to 65–70°C (Scheme 87)[76JCS(P1)989].

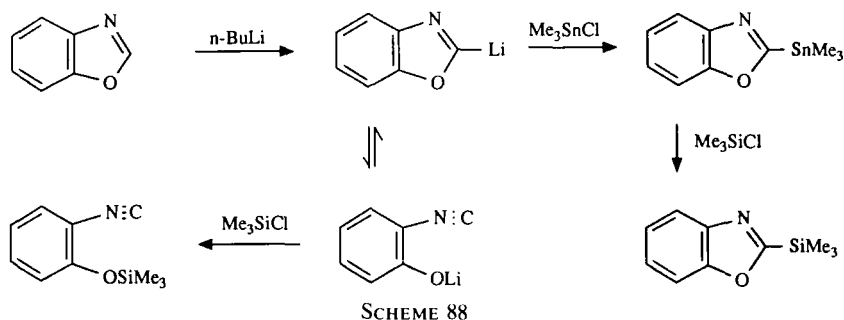


SCHEME 87

4. Benzoxazoles

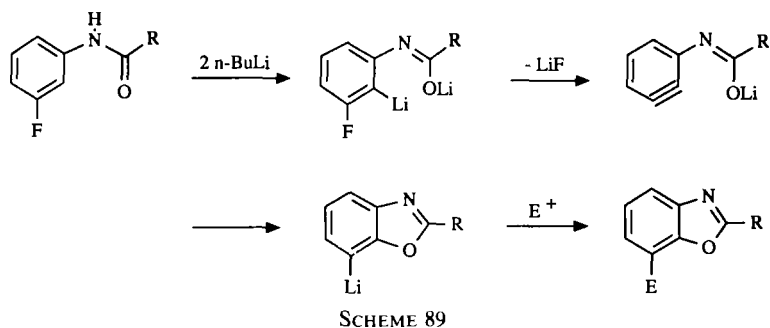
1,2-Benzoxazole undergoes lithiation and fragmentation analogous to that shown by its monocyclic analog, and again either ring-closed or ring-opened products can be obtained depending upon the nature of the

electrophile [83JOM(246)159]. Thus whereas trimethyltin chloride gives the desired 2-substituted benzoxazole, the analogous silyl compound gives the ring-opened derivative (Scheme 88). However, although 2-trimethyl-

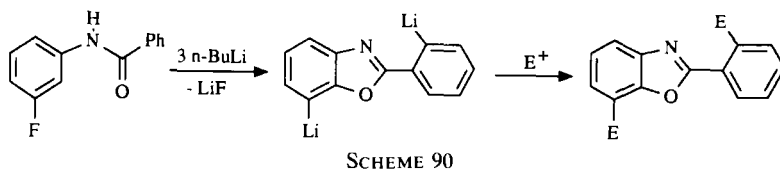


silylbenzoxazole cannot be prepared directly by the lithiation of benzoxazole, it can be obtained indirectly via the stannyl compound merely by heating the latter with trimethylsilylchloride (TMSCl)[83JOM(246)159].

The intramolecular trapping of a benzyne intermediate has been used as a novel route to 7-lithiated benzoxazoles (Scheme 89)(82JOC2804).



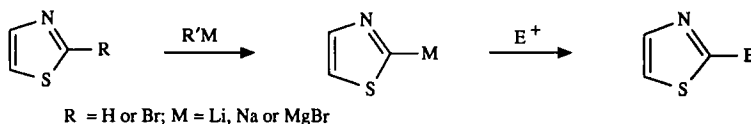
Appreciable *ortho*-lithiation was observed when the exocyclic substituent was a phenyl group, and complete dilithiation could be achieved by using three equivalents of base (Scheme 90).



C. THIAZOLES

1. *Thiazole 2-Carbanions*

By analogy with oxazoles and N-substituted imidazoles, thiazoles and benzothiazoles unsubstituted at C-2 undergo direct metalation at that position, with sodium, lithium, or magnesium reagents (Scheme 91)[79MI1;

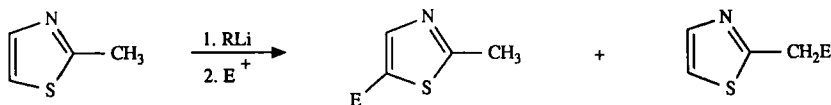


SCHEME 91

84MI3; 88CHE117, 88KGS147), although in certain cases, such as with thiazole itself, halogen-metal exchange can represent a better route because of the easier availability of the starting material (54RTC325). Ring cleavage of the type shown by oxazole is not seen with the thiazole system.

2. *Thiazole 5-Carbanions*

When the 2-position of thiazole is blocked, metalation occurs at the 5-position, although in the case of a methyl group, mixtures are obtained due to lateral metalation (Scheme 92)(67BSF4134; 73JA3408; 74JOC1192).

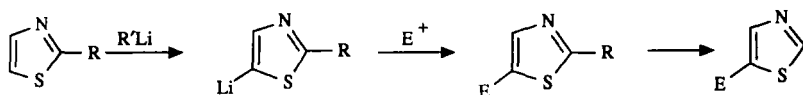


SCHEME 92

However, unlike the situation seen with 2-methyloxazole and 1,2-dimethylimidazole where side-chain metalation predominates, lithiation at C-5 can still be the predominant mode of reaction in certain cases, due to the stronger activating effect of the sulfur atom. The nature of the substituent at C-4, the type of electrophile employed, the temperature of the reaction, and the type of base used can all affect the product ratio (74JOC1192).

With C-2 substituents other than methyl, clean reaction occurs at C-5. Reaction in the presence of a 2-bromine atom has even been achieved using LDA as the base [86JOC1184; 88CJC1617; 92JCS(P1)215]. If the 2-

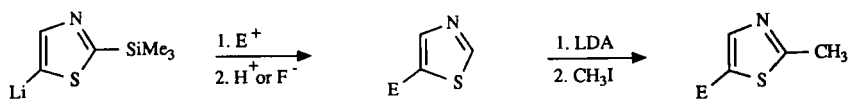
substituent is able to be removed subsequent to the functionalization at C-5 then the overall sequence represents an efficient route to 5-monosubstituted thiazoles (Scheme 93).



SCHEME 93

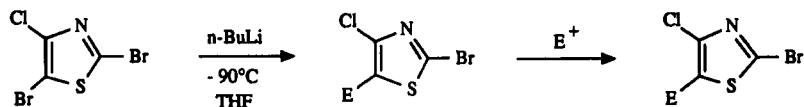
Blocking groups employed have included chloro, removed by zinc and acetic acid (73JOC3316), trimethylsilyl, removed by aqueous acid or fluoride ion (86S757; 87S998; 88CJC1617, 88JOC1748), and bromine, removed by halogen-metal exchange followed by aqueous workup (88CJC1617). In addition, replacement of a 2-chloro substituent has also been achieved with lithium dialkylamides, to give 5-substituted 2-dialkylamino derivatives [90JCS(P1)329]. In contrast, primary amino derivatives can be obtained by the metalation, functionalization, and subsequent hydrolysis of protected 2-aminothiazoles. 2-Amino protection has been successfully achieved with *N,N*-bis(trimethylsilyl) (88CJC1617), and *N*-trifluoroacetyl derivatives (91JHC1017), with the latter compound reacting as the *N*,5-dianion.

Halogen-metal exchange with 5-bromothiazole can be used to give the 2-unsubstituted thiazole-5-anion, but low product yields are obtained after treatment with electrophiles (54RTC325; 88JOC1748). However, because of the facile hydrolysis of the silyl group, much better overall yields are obtained when 2-trimethylsilylthiazole is used as the source of the 5-anion (86S757; 87S998; 88CJC1617, 88JOC1748), and this is the method of choice when 2-unsubstituted derivatives are desired. Further lithiation at C-2 can be used to give 2-alkyl derivatives (Scheme 94) that are not readily available by direct methods because of lateral metalation problems (88CJC1617).



SCHEME 94

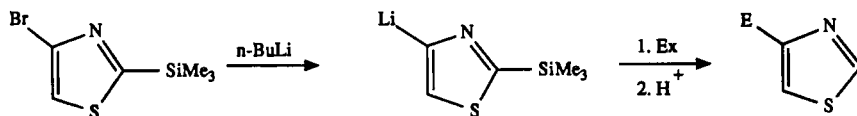
Selective halogen-metal exchange at the 5-position has been achieved with 2,5-dibromo-4-chlorothiazole at $-90^\circ C$ in THF (Scheme 95), although the results obtained were very dependent upon the nature of the electrophile used [92JCS(P1)215].



SCHEME 95

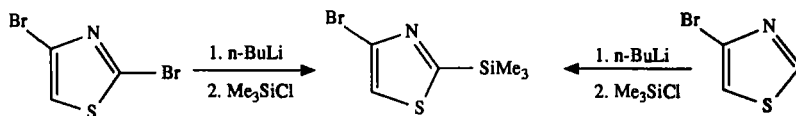
3. Thiazole 4-Carbanions

As would be expected by analogy with imidazoles and oxazoles, the metalation of thiazoles at the 4-position is less facile than that at the 2- or 5-position, although reaction can still be achieved using halogen-metal exchange, provided that the 2-position is blocked. Thus 4-bromo-2-trimethylsilylthiazole gives 4-substituted derivatives in good yield, and these are easily desilylated to give monosubstituted derivatives (Scheme 96)(86S757; 87S998; 88JOC1748).



SCHEME 96

The silylated starting material can be prepared either by selective halogen-metal exchange on 2,4-dibromothiazole or by direct metalation of 4-bromothiazole (86S757; 88JOC1748), with the latter reaction demonstrating the preference for deprotonation at C-2 over halogen-metal exchange at C-4 (Scheme 97).

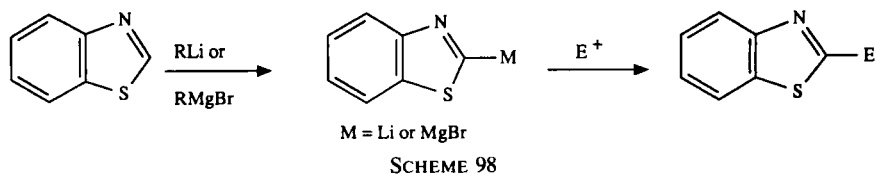


SCHEME 97

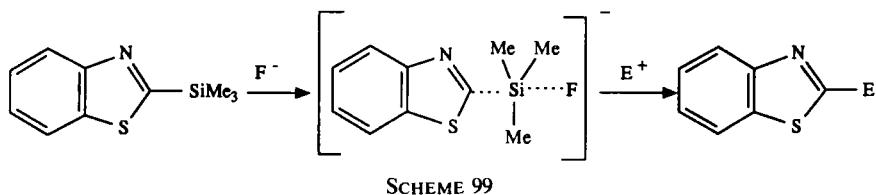
4. Benzothiazoles

In a manner similar to that of thiazole itself, benzothiazole undergoes metalation at C-2 with sodium, magnesium, or lithium reagents [43CR(217)231; 49JA2328; 69JGU1816] and reaction with a variety of electrophiles can then be achieved in good yield (Scheme 98)(79OR1; 85H295; 88BCJ3637, 88H2659).

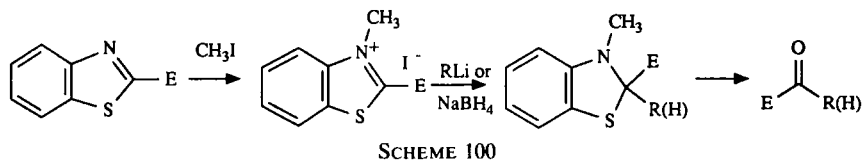
Fluoride-catalyzed desilylation of 2-trimethylsilylbenzothiazole has also



been used as a source of a benzothiazole-2-anion (Scheme 99) but the method appears to offer no advantage over direct metalation except in the case of α,β -unsaturated enones such as 2-cyclohexenone where conjugate (1,4-) rather than 1,2-addition occurred (82TL5079).

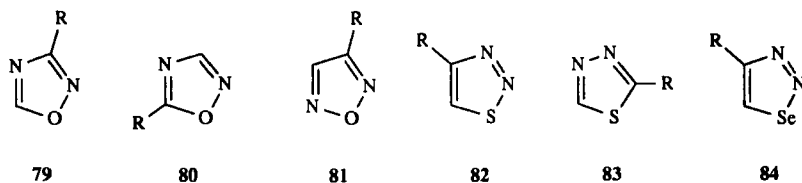


One of the reasons that the 2-lithiobenzothiazole system has received attention is the ability of the benzothiazole group to act as a synthon for an aldehyde or ketone group (78TL5; 85H295; 88BCJ3637). Thus, after reaction of the anion with an electrophile, the product is alkylated with methyl iodide followed by the nucleophilic addition of either an alkyl group or a hydride ion. Subsequent hydrolysis results in the formation of a ketone or an aldehyde (Scheme 100).

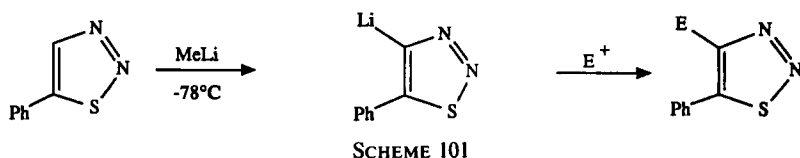


D. OXADIAZOLES, THIADIAZOLES, AND SELENADIAZOLES

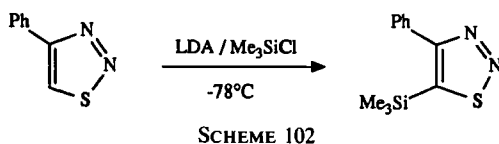
There are few reports on the successful metalation and derivatization of heterodiazoles since these compounds have been found to undergo very facile base-induced ring-cleavage reactions [87AHC(41)41]. Thus 1,2,4-oxadiazoles **79** and **80**, 1,2,5-oxadiazoles **81**, 1,2,3-thiadiazoles **82**, 1,3,4-thiadiazoles **83**, and 1,2,3-selenadiazoles **84** have all been reported to undergo ring-opening reactions[87AHC(41)41].



However, lithiation of 5-phenyl-1,2,3-thiadiazole has been achieved using methyllithium, and reaction with a variety of electrophiles has given good yields of 4-substituted derivatives (Scheme 101)(68CJC1057; 85S945).

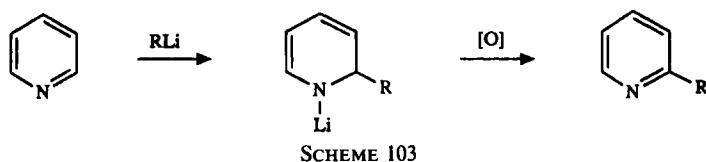


The isomeric 4-phenyl-1,2,3-thiadiazole underwent fragmentation under the same conditions, although successful reaction could be achieved using LDA, provided that chlorotrimethylsilane was present “*in situ*” to trap the 5-anion as it was formed (Scheme 102)(85S945).



IV. Azines

The formation of sp^2 -carbanions adjacent to pyridine-like nitrogen in 6-membered heteroaromatic rings is complicated by the fact that with alkyl and aryllithiums, 1,2-nucleophilic addition to the azomethine double bond (Scheme 103) normally occurs in preference to metalation [88H2659, 88MI2; 88T1; 90H(31)1155; 91AHC(52)187].

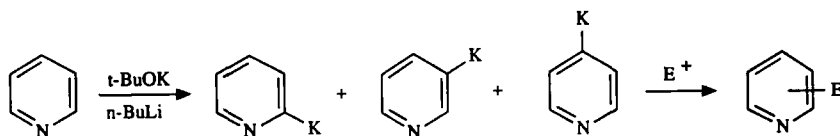


Since addition to the C=N bond is temperature dependent, low-temperature halogen-metal exchange has traditionally been the means of circumventing this problem [51OR339; 74MI1; 88MI2; 91MI9], with organolithium compounds normally being used because poorer results were originally obtained under Grignard reaction conditions, even when the entrainment procedure with ethyl bromide was employed (38RTC179; 40RTC971).

The regiospecific synthesis of substituted azine derivatives by the use of heteroatom directed lithiation has also become a common occurrence in recent years, and this route has led to the successful synthesis of a wide variety of substituted derivatives [87MI1; 88AHC(44)199; 90CRV879; 91AHC(52)187]. The activation and stabilization provided by the heteroatom substituent mean that deprotonation can occur at lower temperatures, and thus the problem of addition to the azomethine double bond is minimized. The utility of this method, and of the different substituent groups involved in the directed metalation process, is detailed in the following sections.

A. PYRIDINES

The direct metalation of pyridine has been achieved by the use of a 1:1 mixture of *n*-BuLi and *t*-BuOK (84CC257, 84JOC3857), with a mixture of 2-, 3-, and 4-substituted derivatives being obtained after reaction with a number of electrophiles (Scheme 104). In all cases the proportion of the

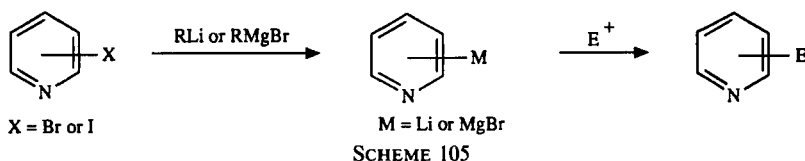


SCHEME 104

3-substituted compound was low, whereas the relative ratios of the 2- and 4-isomers were found to be very dependent on the reaction conditions. Diethyl ether as solvent favors 2-substitution (~90%), and HMPT as cosolvent in THF favors 4-substitution (~85–90%)(84JOC3857).

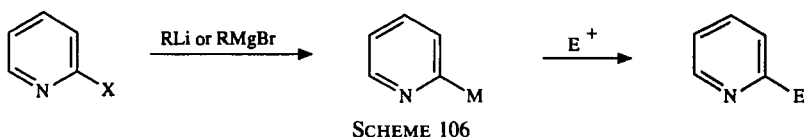
Better results are achieved using halogen-metal exchange, however, and good yields of pyridyl Grignard reagents can be obtained from the reaction of phenylmagnesium bromide with bromopyridines [69AG(E)279], or ethylmagnesium bromide with iodopyridines (87TL5845). An advantage of using Grignard reagents over lithium bases

is that nucleophilic addition to the azomethine double bond occurs less readily, although when it does occur, 1,4-addition is the main mode of reaction (51JA5861). Grignard derivatives have been prepared from chloropyridines, but better results are obtained with the bromo or iodo compounds. Similarly with lithium reagents, halogen-metal exchange occurs readily with bromo or iodopyridines but normally not at all with chloropyridines (Scheme 105).



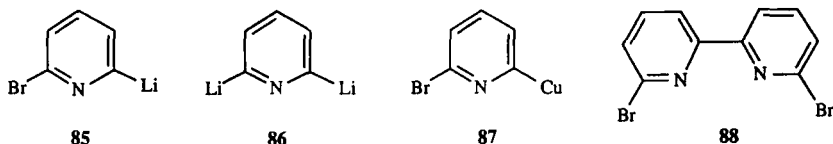
1. Pyridine 2-Carbanions

Pyridine 2-carbanions are the least thermodynamically stable of the three possible anionic derivatives of pyridine because of electrostatic repulsion between the coplanar nitrogen lone-pair electrons and the electron pair of the adjacent anion (69JA5501). However, under kinetically controlled conditions, deprotonation at the α -position can become the most favored mode of reaction, as was shown above by the high proportion of the 2-substituted product obtained from the direct metalation of pyridine with *n*-BuLi and *t*-BuOK in ether (84CC257, 84JOC3857). This result was interpreted as due to a directed metalation involving the pyridine nitrogen in the low polarity solvent, and contrasts with the results obtained in more polar media where 4-substituted derivatives were the major products. However, despite the high proportion of the 2-substituted products formed by this procedure, it is still necessary to remove small amounts of other isomeric products, and the most favorable route to 2-pyridylcarbanions is still via low temperature halogen-metal exchange on 2-bromo or 2-iodopyridines (Scheme 106). After reaction of the appropriate 2-lithium or 2-halomagnesium derivative with various electrophiles, a wide variety of 2-substituted pyridines are available (87MI1, 87TL5845). Transmetalation



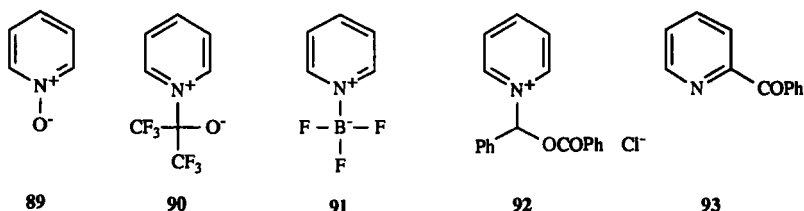
to 2-pyridylcopper derivatives has also been used in certain cases where conjugate addition to enones was desired [82T1509; 83JOM(243)241].

2,6-Dihalopyridines have also been investigated as sources of α -pyridyl carbanions, and under the appropriate conditions either mono- or dimetallic derivatives can be obtained. Thus, 2,6-dibromopyridine gives the monolithio derivative **85** on treatment with *n*-BuLi in ether [51JOC1485; 73JOM(56)53], whereas in THF the dilithio derivative **86** can be obtained, either from the dibromo- or the diiodopyridine [80JOM(186)147]. A dimetallic derivative can also be obtained from the dibromide using magnesium and ethyl bromide (entrainment procedure) [40RTC971], and this compound is stable at ambient temperatures, whereas the analogous dilithio compound was unstable above -80°C [80JOM(186)147]. Transmetalation of the monolithio derivative **85** to the analogous copper compound **87** has also been achieved, with subsequent coupling giving rise to the dibromobipyridyl derivative **88** [73JOM(56)53]. Dual lithium-bromine exchange on this compound was also successfully performed, to give rise to a variety of 6,6'-disubstituted-2,2'-bipyridyls [73JOM(56)53].



Although 2-bromo- or 2-iodopyridines provide a good route to 2-pyridyl metal derivatives, it is still necessary to prepare the halopyridine, and although this is often a trivial matter with pyridine itself, the same is not true of substituted derivatives. Therefore a number of other methods have been investigated in order to activate the substituted pyridine so that direct metalation can occur. One of these methods involves substitution on the pyridine nitrogen, since this enhances reactivity at the 2- and 6-positions because of the adjacent positive charge. Thus, pyridine *N*-oxides **89** are selectively metalated at the 2-position more readily than the parent compounds (67JA1537), but 2,6-disubstitution is often a side reaction and product yields are generally not very high (72JOC1690, 72JOC3584). However, clean metalation at the 2-position can be achieved with the hexafluoroacetone and BF_3 complexes **90** and **91**, provided that the nonnucleophilic lithium tetramethylpiperidide (LiTMP) is used as the base at low temperature (83JOC4156; 91CC570). The added groups function not only by increasing the acidity of the adjacent 2- and 6-protons, but also by stabilizing the lithio derivative once formed. Loss of the complexing groups occurs readily during the workup of the reaction to give 2-substi-

tuted pyridine derivatives. A similar metalation at the 2-position of **92** occurs with sodium bis(trimethylsilyl)amide; complex **92** is itself formed by reaction of pyridine with an aldehyde and an acid chloride (84TL1715; 86CB279). In this case metalation is followed by an intramolecular acylation to give the 2-pyridyl ketone **93**. Pyridyl 2-esters can also be obtained by this method if chloroformates are used in place of the acid chloride.

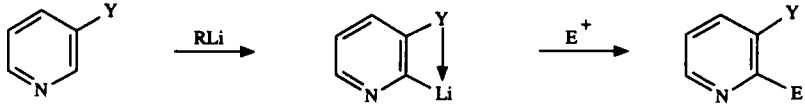


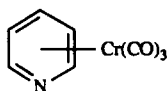
However, an area that has received a lot of attention in recent years involves the direct metalation of 3-substituted pyridines, which can occur at either the 2- or the 4-positions, depending on the metalation conditions and nature of the substituent [91AHC(52)187]. As with the direct metalation of pyridine itself the 4-metalated derivative is favored thermodynamically, although the 2-metalated derivative can be obtained under kinetic conditions. Thus pyridines that possess weak chelating groups at the 3-position, such as halogen and alkoxy, are able to be successfully lithiated at C-2 using strongly basic conditions at low temperature. Provided that the electrophile is added while the low temperature of the metalation reaction is maintained, 2,3-disubstituted pyridines can successfully be obtained (Table VIII).

If the reaction mixture is allowed to warm before addition of the electrophile, then isomerization to the more thermodynamically stable 4-metalated derivative can result in the formation of 3,4-disubstituted products. However, if the 4-position is already substituted then metalation and subsequent reaction at C-2 are much easier to achieve, and a wider range of metalation conditions can be used. Direct 2,4-disubstitution can be achieved in those cases where the electrophile is stable in the presence of the base. Normally this involves the use of LDA in the presence of chlorotrimethylsilane. In this case metalation and substitution occur first at C-4 followed by reaction at C-2.

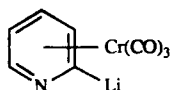
The tricarbonylchromium (0) complex of pyridine **94** has also recently been shown to undergo selective lithiation at the C-2 position with LDA, to give **95** [JCS(P1)501]. However, this result is not synthetically significant since the starting material **94** was actually prepared by desilylation of the 2,6-disubstituted derivative **96**.

TABLE VIII
SYNTHESIS OF 2,3-DISUBSTITUTED PYRIDINES VIA DIRECTED METALATION
OF 3-SUBSTITUTED DERIVATIVES

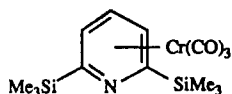
					
Y	Metalation conditions	Electrophile	Yield (%)	Reference	
F	<i>n</i> -BuLi/TMEDA/Et ₂ O/ -75°C	TMSCl	73 ^a	83T2009 ^b	
	<i>n</i> -BuLi/DABCO/Et ₂ O/ -60°C	TMSCl	80	83T2009	
Cl	<i>n</i> -BuLi/TMEDA/Et ₂ O/ -60°C	TMSCl	60 ^c	81JOM(216)139	
OMe	<i>n</i> -BuLi/TMEDA/THF/ -40°C	MeCHO	49	82S235	
	MesLi/THF/ -23°C	Various	73–85	88TL773	
OEt	<i>n</i> -BuLi/TMEDA/THF/ -40°C	Various	27–83	82S235	
OCH ₂ Ph	<i>n</i> -BuLi/TMEDA/THF/ -40°C	TMSCl	44	82S235	
OTMS ^d	LDA/THF/ -78°C	TMSCl ^e	85	91CB2119	
F, 4-Cl	<i>n</i> -BuLi/THF/ -40°C	Et ₃ CO	40	72CR(C)(275)1535	
F, 4-TMS ^f	LDA/THF/ -75°C	TMSCl	70	83T2009	
Cl, 4,5,6-Cl	LDA/Et ₃ O/ -75°C	I ₂	23	79JCS(P1)1472	
Cl, 4-TMS ^f	LDA/THF/ -60°C	TMSCl	65	81JOM(216)139 ^g	
Br, 4-TMS ^f	LDA/THF/ -78°C	TMSCl	52	91CB2119	
OCONEt ₂ , 4-TMS	LiTMP/THF/ -78°C	Various	39–89	91AHC(52)187	
	LDA/THF/ -78 → 25°C	CONEt ₂ ^h	58	92H(33)533	
OCSNEt ₂ , 4-TMS	LiTMP/THF/ -78 → 25°C	CSNEt ₂ ^h	75	92S112	
OSEM ⁱ , 4-TMS	<i>t</i> -BuLi/Et ₂ O/ -78°C	PhCHO	82 ^j	90TL4267	
OMe, 5-CH(OLi)NR ₂ ^k	MesLi/THF/ -42 → 0°C	Mel	79	90JOC69	

^a 6% 4-substituted product also obtained.^b See also 72CR(C)(275)1535.^c 9% 4-substituted product also obtained.^d Formed *in situ* from 3-hydroxypyridine.^e *In situ* reaction conditions.^f Trimethylsilyl (TMS) group added via *in situ* reaction.^g See also 91CB2119.^h Anionic *ortho*-Fries rearrangement.ⁱ 2-(Trimethylsilyl)ethoxymethoxy.^j Trimethylsilyl group subsequently removed selectively in 90% yield.^k NR₂ = *N*-methylpiperazinyl.

94



95



96

2. Pyridine 3-Carbanions

The formation of pyridine 3-carbanions is thermodynamically a more favorable process than that for the 2-analogs, and this is exemplified by the exchange reaction between 2-lithio- and 3-bromopyridines (Scheme 107), which occurs readily at -100°C (77JOC257).

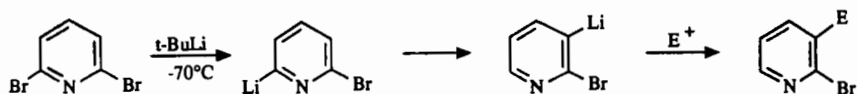


SCHEME 107

Because of this greater propensity for β - rather than α -carbanion formation, selective halogen-metal exchange of β -halogens in α,β -halopyridines can readily be achieved. Thus both 2,3-dibromo- (85T3433) and 2,5-dibromopyridine (77JOC257) undergo exclusive replacement of the β -halogen on reaction with *n*-BuLi at low temperatures to give **97** and **98**, respectively. Selective replacement of one of the two bromine atoms in 3,5-dibromopyridine has also been achieved with *n*-BuLi to give **99** (51JOC1485). 3-Pyridyl Grignard reagents **100** are also readily available, either by the reaction of EtMgBr with 3-iodopyridine (87TL5845) or from reaction of PhMgBr with 3-bromopyridine [69AG(E)279] or 3-phenylsulfonylpyridine **101** (86TL3899).



Low temperatures are necessary with *ortho*-halolithiopyridines in order to prevent pyridyne formation, and an added complication with some bromopyridines is that rearrangement of the initial lithio derivative can occur via an intermolecular transmetalation process (Scheme 108) (79T1625; 85T3433). This result has been used synthetically to give 2-bromo-3-substituted derivatives from 2,6-dibromopyridine [90JOM-

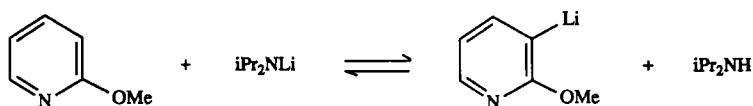


SCHEME 108

(382)319]. The rearrangement step is accelerated by the addition of trace amounts of 2-bromopyridine and diisopropylamine, which serve as transfer agents for the lithium atom.

However, by far the most useful route to 3-pyridyl carbanions is via directed metalation [91AHC(52)187], which can be achieved by the lithiation of either 2- or 4-heterosubstituted pyridines (Tables IX and X).

The range of metalation conditions that can be used is more varied than that for α -carbanion formation (Table VIII), since isomerization to a more thermodynamically stable carbanion is no longer a problem. Thus, LDA is now able to be used as the base in many cases, with the major advantages being that it does not undergo nucleophilic addition to the pyridine azomethine group or induce halogen-metal exchange reactions with brominated derivatives (72TL3507). Complete reaction is normally not seen with LDA and 2- or 4-methoxypyridine, however, as an equilibrium is established with the lithiated pyridine and the free amine (Scheme 109).



SCHEME 109

Good yields of products can still be obtained with electrophiles such as chlorotrimethylsilane which are relatively stable in the presence of LDA (88TL773), but poor results are seen with other electrophilic substrates.

The equilibrium problem has been overcome in the case of 2-methoxypyridine by the addition of MeLi, which deprotonates the diisopropylamine as it forms, thereby driving the equilibrium to the right (88JOC1367). Only a catalytic amount (ca. 5%) of LDA is required since it is continually regenerated during the reaction. MeLi is normally used for this method since it does not undergo competitive addition to the azomethine bonds, and by itself only gives very slow deprotonation, although more recently PhLi has also been employed [91JOM(406)49]. Catalytic metalation is not necessary with 2,4-dialkoxypyridines, however, as the extra activation provided by the second substituent results in ready metalation occurring with LDA at the 3-position (90JOC2964). Other 2,4-disubstituted derivatives also readily undergo metalation at the 3-position, as do a number of other disubstituted pyridines that possess at least one lithiation directing group at either the 2- or the 4-position (Table XI).

Pyridine aldehydes can also be lithiated at C-3, provided that the aldehyde functionality is first converted to its α -aminoalkoxide derivative by reaction with the lithium salt of an amine (90JOC69). In a study with

TABLE IX
SYNTHESIS OF 2,3-DISUBSTITUTED PYRIDINES VIA DIRECTED METALATION
OF 2-SUBSTITUTED DERIVATIVES

Y	Metalation conditions	Electrophile	Yield (%)	Reference
F	<i>n</i> -BuLi/THF/ -40°C LDA/THF/ -70°C	Et ₂ CO Various	25 43-95	72CR(C)1535 ^a 81JOM(215)139 ^b
Cl	PhLi/DIA ^c /THF/ -40°C LDA/THF/ -78°C LDA/THF/ -70°C	R ₂ NCHO ^d R ₃ SiCl Various	60 47-74 21-66	91JOM(406)49 80TL4137; 90JOC292 90JCS(P1)2409
Br	PhLi/DIA ^c /THF/ -40°C ^e LDA/THF/ -70°C	Various	30-80 13-58	91JOM(406)49 82JCR(M)2863, 82JCR(S)278 ^f
CONHMe	<i>n</i> -BuLi/THF/ -78°C	Various	49-66	81S127 ^g
CONHCH ₂ Ph	<i>n</i> -BuLi/THF/ -78°C	Various	61-89	81S127 ^g
CONHPh	<i>n</i> -BuLi/THF/ -78°C <i>n</i> -BuLi/TMEDA/Et ₂ O/ -78 → 0°C	Various ArCHO	33-95 51-58 ⁱ	86JCR(M)442, 86JCR(S)20 ^h 90SC2623 ^j
CONEt ₂	LDA/Et ₂ O/ -78 → RT	CONEt ₂ ^k	94	86JCR(M)401, 86JCR(S)18 ⁱ
CON(iPr) ₂	LDA/Et ₂ O/ -78°C	Various	13-76	86JCR(M)401, 86JCR(S)18 ⁱ
Ar- <i>o</i> -CON(iPr) ₂	LDA/THF/0°C → RT	CON(iPr) ₂ ^m	90	91JOC1683
Imidazolinone ⁿ	MeLi/THF/ -78°C	Various		86EUP166907
NHCO- <i>t</i> -Bu	<i>n</i> -BuLi/THF/ -78 → 0°C <i>n</i> -BuLi/TMEDA/Et ₂ O/ -10°C	Various	54-87 70-90	83JOC3401 ^o 89JHC105 ^p
NHCO ₂ - <i>t</i> -Bu	<i>t</i> -BuLi/THF/ -78 → 20°C	R ₂ NCHO ^d	58	88JMC2136
OMe	LDA/THF/0 or 25°C MeLi/THF/0°C MeLi/DIA ^c /THF/ -40 → 0°C	TMSCl ^q Various Various	83,100 62-66 15-70	88JOC1367, 88TL773 88TL773 88JOC1367 ^r
OCONEt ₂	<i>s</i> -BuLi/TMEDA/THF/ -78°C	Various	52-72	85JOC5436 ^s
OSiMe ₃ ^t	LDA/THF/ -78°C	TMSCl ^u	41	91CB2119
S-Bt ^v	LDA/THF/ -78°C	Various	52-66	87H(26)427
SO- <i>t</i> -Bu	LDA/THF/ -78°C	Various	20-90	92TL2625
SOPh	LDA/THF/ -78 → 0°C	Various	50-90	89TL7091 ^w
SO ₂ NR ₂ ^d	LDA/THF/ -70°C	Various	55-95	87JOC1133 ^x

^a See also 81JOC4494.

^b See also 88JOC2740.

^c 5% diisopropylamine added to give catalytic amount of LDA.

^d R₂N = piperidinyl.

^e Temperature lowered to -70°C prior to addition of some electrophiles.

^f See also 91CB2119.

^g See also 86JCR(M)442, 86JCR(S)20.

^h See also 83TL4735.

ⁱ Yield of lactone derived from treatment of initial hydroxy product with 10% H₂SO₄.

^j See also 90M909.

^k Intermolecular condensation.

^l See also 80TL4739.

^m Intramolecular condensation.

ⁿ 2-(5-isopropyl-5-methyl-4-imidazolinone).

^o See also 84TL2127, 88TL5725, 90JOC4744.

^p See also 88JOC2740.

^q Very poor yield with other electrophiles.

^r See also 91JOM(406)49 for use of PhLi.

^s See also 88BSF67 and 90CRV879.

^t Formed *in situ* from 2-pyridone.

^u *In situ* reaction.

^v Benzothiazolyl-2-thio.

^w See also 91TL2943 and 91TL2947.

^x See also 92JHC61.

TABLE X
SYNTHESIS OF 3,4-DISUBSTITUTED PYRIDINES VIA DIRECTED METALATION
OF 4-SUBSTITUTED PYRIDINES

Y	Metalation conditions	Electrophile	Yield (%)	Reference
F	<i>n</i> -BuLi/THF/ -40°C LDA/Et ₃ O/ -70°C	Et ₃ CO ArCHO	65 65–80	72CR(C)1535 88JHC81
Cl	<i>n</i> -BuLi/THF/ -40°C LDA/THF/ -78°C LDA/Et ₃ O/ -70°C	Et ₃ CO ArCHO, R ₃ SiCl Various	60 60–93 30–90	72CR(C)1535 86S886; 90JOC292 ^a 88JHC81
CONHPh	<i>s</i> -BuLi/TMEDA/Et ₃ O/ -78°C <i>n</i> -BuLi/THF/ -78 → 0°C <i>n</i> -BuLi/TMEDA/Et ₃ O/ -78 → 0°C	D ₂ O Various ArCHO	100 16–87 ^b 61–78 ^d	80H1649, 80JA1457 86JCR(M)442, 86JCR(S)20 ^c 90SC2623 ^c
CONEt ₂	<i>s</i> -BuLi/TMEDA/Et ₃ O/ -78°C <i>s</i> -BuLi/TMEDA/THF/ -78°C LDA/Et ₃ O/ -45°C	D ₂ O DMF CONEt ₂ ^f	55 38 75	80H1649, 80JA1457 86JOC3325 86JCR(M)401, 86JCR(S)18 ^g
CON(iPr) ₂	<i>s</i> -BuLi/TMEDA/Et ₃ O/ -78°C LDA/Et ₃ O/ -78°C	D ₂ O Various	95 25–96	80H1649, 80JA1457 86JCR(M)401, 86JCR(S)18 ^g
Oxazoline ^h	MeLi/THF/ -78 → 0°C	Various	27–83	78TL227; 82JOC2633
Ar- <i>o</i> -CONEt ₂ ⁱ	LDA/THF/RT	CONEt ₂ ⁱ	76	92JOC424
NHCO- <i>t</i> -Bu	<i>n</i> -BuLi/THF/ -78 → 0°C <i>n</i> -BuLi/TMEDA/Et ₃ O/ -10°C	Various Various	60–94 60–95	83JOC3401 ^k 89JHC105 ^l
NHCO ₂ - <i>t</i> -Bu	<i>t</i> -BuLi/THF/ -78 → -20°C	RCHO	14–57	84CC1304 ^m
OMe	LDA/THF/0°C MeLi/THF/ -23°C	TMSCl Various	61 ⁿ 65–84	88TL773 88TL773
OCH ₂ CH ₂ OMe	LDA/THF/ -70°C	TMSCl	39	85CPB1016
OCONEt ₂	<i>s</i> -BuLi/TMEDA/THF/ -78°C <i>s</i> -BuLi/TMEDA/THF/ -78°C → RT	Various CONEt ₂ ^p	37–72 74	85JOC5436 85JOC5436
OSiMe ₃ ^q	LDA/THF/ -78°C	TMSCl ^q	41	91CB2119
SO- <i>t</i> -Bu	LDA/THF/ -78°C	Various	66–74	92TL2625
SOPh	LDA/THF/ -78 → 0°C	PhCHO, TMSCl	67, 81	89TL7091
SO ₂ NR ₂ ^r	LDA/THF/ -70°C	Various	75–95	87JOC1133 ^s

^a See also 80TL4137.

^b Includes *N*-methylated product.

^c See also 83TL4735 and 91SC85.

^d Yield of lactone derived by treatment of hydroxy product with 10% H₂SO₄.

^e See also 90M909.

^f Intermolecular condensation.

^g See also 80TL4739.

^h 4,4-Dimethyl-2-oxazoline.

ⁱ 3'-TMS blocking group also present.

^j Remote anionic Fries rearrangement.

^k See also 88TL5725, 90JOC4744.

^l See also 88JOC2740.

^m See also 88JMC2136 and 88TL5725.

ⁿ Accompanied by 16% 3,5-disilylated material; other electrophiles low yield.

^o 4-Pyridone product via anionic Fries rearrangement.

^p Formed *in situ* from 4-pyridone.

^q *In situ* reaction conditions.

^r NR₂ = piperidinyl.

^s See also 92JHC61.

TABLE XI
SYNTHESIS OF POLYSUBSTITUTED PYRIDINES VIA DIRECTED METALATION
AT THE 3-POSITION

Substituents	Metalation conditions	Electrophile	Yield (%)	Reference
2,4,6-F ₃	<i>n</i> -BuLi/hexane/ -60°C	CO ₂	65	65JCS5045
2,4,5,6-F ₄	<i>n</i> -BuLi/Et ₂ O/ -70°C	PhN(Me)CHO	40	69JCS(C)1700
2-F	LDA/THF/ -75°C	Various	50-80	92JOC565
4-C[O(CH ₂) ₃ O]Me				
2,4-Cl ₂	<i>n</i> -BuLi/THF/ -80°C	PhCHO	74	91JOC4793
	LDA/THF/ -80°C	Various	55-85	91JOC4793
2,4,5,6-Cl	<i>n</i> -BuLi/Et ₂ O/ -75°C	Br ₂ , I ₂	58, 60	79JCS(P1)1472 ^a
2-Cl	<i>n</i> -BuLi/THF/ -78°C	Various	61-93 ^b	91T1697
4-CONHPh				
2-Cl	LDA/THF/ -70°C	ArCHO	59-72	87CJC2027; 88H1671
4-C(OCH ₂) ₂ Me				
2-Cl	MeLi/THF/ -70°C	ArCHO	40-62	84CC897
4-Oxazoline ^d				
2-OMe	<i>n</i> -BuLi/TMEDA/THF/ -78 → 23°C	MeI, ArCHO	67 ^c , 62	89T7469
4-CONHPh				
2-OMe	MeLi/THF/ -5°C	ArCHO	62-75	87S142
4-Oxazoline ^d				
2-CONHPh	<i>n</i> -BuLi/THF/ -78°C	Various	48-84 ^c	91T1697
4-Cl				
2-CONHPh	<i>n</i> -BuLi/TMEDA/THF/ -78 → 23°C	MeI, ArCHO	76, 71	89T7469
4-OMe				
2-NHCO- <i>t</i> -Bu	<i>t</i> -BuLi/Et ₂ O/ -78°C	Me ₂ S ₂	74	83JOC3401
4-Me				
2-NHCO- <i>t</i> -Bu	<i>t</i> -BuLi/THF/ -78°C	Me ₂ S ₂	86	83JOC3401
5-Cl				
2-NHCO- <i>t</i> -Bu	<i>t</i> -BuLi/Et ₂ O/ -78°C	Me ₂ S ₂	70	83JOC3401
6-F				
2,4-OR ₂ ^f	LDA/DME/ -78°C	CO ₂	51-95 ^k	90JOC2964 ^h
5-CO ₂ Et, 6-CF ₃				
2-OMe	<i>t</i> -BuLi/TMEDA/THF/ -78 → 42°C	MeI	70 ^j	90JOC69
5-CH(OLi)NR ₂ ⁱ				
4-Br	LDA/THF/ -78°C	TMSCl	65	85JOC5436
5-CONEt ₂				
4-OMe	MesLi/THF/ -23°C	MeI	82	90JOC69
5-CH(OLi)NR ₂ ⁱ				
4-CONEt ₂	<i>s</i> -BuLi/TMEDA/THF/ -78°C	TMSCl	66	85JOC5436
5-OCONEt ₂				
4-OCONEt ₂	<i>s</i> -BuLi/TMEDA/THF/ -78°C	TMSCl	68	85JOC5436
5-CONEt ₂				
4-OCONEt ₂	<i>s</i> -BuLi/TMEDA/THF/ -78°C	CONEt ₂ ^k	60	85JOC5436
5-TMS				
2,6-Cl ₂	LDA/THF/ -80°C	Various	56-76 ^l	91JOC4793
	PhLi/DIA ^m /THF/ -40°C	R ₂ NCHO ⁿ	55	91JOM(406)49

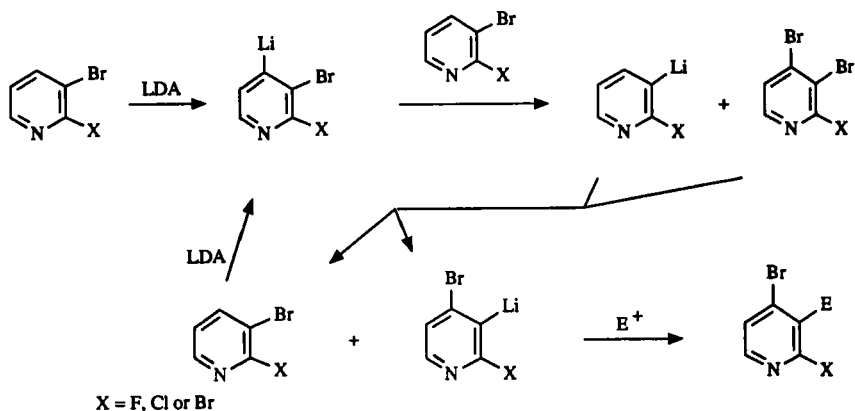
TABLE XI (Continued)

Substituents	Metalation conditions	Electrophile	Yield (%)	Reference
2,6-OMe ₂	<i>n</i> -BuLi/THF/ - 78 → 10°C	ClCH ₂ OMe	96	90H(31)505
	PhLi/DIA ^m /THF/ - 40°C	R ₂ NCHO ⁿ	55	91JOM(406)49
2-OMe	<i>t</i> -BuLi/THF/ - 78 → 42°C	MeI	70 ^j	90JOC69
6-CH(OLi)NR ₂ ⁱ				
2-CH(OLi)NRR' ^o	<i>n</i> -BuLi/THF/ - 78 → 42°C	MeI	77 ^j	90JOC69
6-OMe				
2-CH(OLi)NRR' ^o	<i>n</i> -BuLi/THF/ - 42 → 23°C	MeI	67 ^j	90JOC69
5-Me, 6-OMe				
2-CONH- <i>t</i> -Bu	<i>n</i> -BuLi/THF/0°C	MeOCH ₂ NCS	88	84TL2127
6-CONH ₂				

^a See also 73JCS(P1)1125.^b Reaction with MeI gave solely *C,N*-dimethyl derivative in 83% yield.^c *C,N*-dimethylated product.^d 4,4-Dimethyl-2-oxazoline.^e Reaction with MeI gave a mixture of the *C*-monomethyl (65%) and *C,N*-dimethyl (19%) derivatives in 84% total yield.^f R = Me, Et, *i*Pr.^g Yields inversely proportional to the size of the alkyl group.^h See also 91JOC5726.ⁱ NR₂ = *N*-methylpiperazinyl.^j Trace of other isomer also obtained.^k 4-Pyridone product via anionic Fries rearrangement.^l Isolated yield after chromatographic removal of 4-isomer.^m Diisopropylamine.ⁿ NR₂ = piperidinyl.^o NRR' = N(Me)CH₂CH₂NMe₂.

methoxypyridinecarboxaldehydes, it was found that the methoxy group determined the position of lithiation when the sterically bulky *N*-methylpiperazine group was used as the amine component, but that metalation occurred adjacent to the protected aldehyde functionality when the acyclic *N,N,N'*-trimethylethylenediamine was employed (90JOC69).

With some bromopyridines it is possible to get migration of the bromine atom by an intermolecular "halogen dance" mechanism (79T1625; 82T3035; 86T2252) that is analogous to that seen with polybromobenzenes under basic conditions (72ACR139). An example is the rearrangement of 3-bromo-2-halopyridines to 4-bromo-2-halo-3-lithio derivatives, which can then be reacted with electrophiles in 20–80% yield [90JOM(382)319; 92JOC565]. Apart from the initial lithiation at the 4-position the sequence involves a series of halogen–metal exchange reactions, which lead to the thermodynamically more stable 2,4-dihalo-3-lithio derivative (Scheme 110).



SCHEME 110

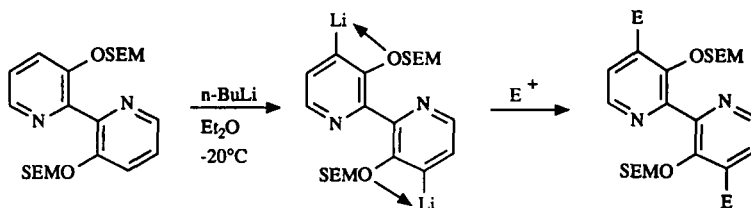
3. Pyridine 4-Carbanions

As with the 2- and 3-pyridyl systems, halogen-metal exchange reactions can also be used as a source of 4-pyridyllithiums and Grignard reagents (55RTC1003; 87TL5845), although this is complicated by the fact that nucleophilic substitution of a 4-bromine atom is easier than has been recognized (85T3433). The Grignard derivative has also been prepared from 4-pyridyl phenyl sulfoxide by displacement of the sulfoxide with PhMgBr (86TL3899). Preferential formation of the 4-isomer is also observed in the direct metalation of pyridine under polar conditions, and this was shown to be the result of equilibrium effects that give rise to the more thermodynamically stable derivative (84JOC3857). A similar preference for the 4-substituted derivative is observed in the direct metalation of 3-substituted pyridines under thermodynamic conditions [91AHC(52)187], even in those cases (e.g., 3-fluoro) where initial kinetic lithiation at the 2-position still occurs (83T2009)(Table XII). The preference for 4-metalation is further reinforced by the lithiation of 2,5-dichloropyridines that fail to metalate at the 3-position even though this site would be favored in the absence of the 5-substituent.

With electron-withdrawing 3-substituents, such as the 5,5-dimethyl-2-oxazoline group, nucleophilic 1,4-addition of alkylolithiums occurs readily (78H133; 82JOC2633; 85T837). However, this can often be overcome by the use of nonnucleophilic amide bases such as LiTMP , although dimerization of the starting material can still occur under these conditions [91JCS(P1)3165]. The use of other acid derivatives such as secondary

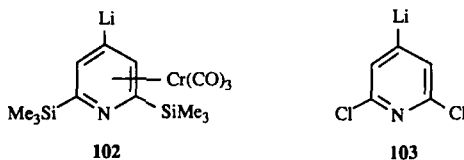
amides, which undergo preferential deprotonation rather than nucleophilic addition, usually overcomes these problems, however.

The facility for 4-metalation shown by 3-substituted pyridines is continued with bipyridyl derivatives, and thus 3,3'-bis[2-(trimethylsilyl)ethoxy]-methyl-2,2'-bipyridine gave the 4,4'-dilithio species on treatment with *n*-BuLi, and this then afforded 4,4'-disubstituted bipyridines, often in very good yield (Scheme 111)(88HCA957).



SCHEME 111

Direct metalation of 2,6-disubstituted pyridines has also been reported to occur at the 4-position under certain conditions. Thus the 2,6-bis(trimethylsilyl) chromium tricarbonyl compound **96** gave the 4-lithio derivative **102** [91JCS(P1)501], and 2,6-dichloropyridine gave mainly the 4-lithio derivative **103** under kinetic deprotonation conditions, in contrast to the thermodynamic situation where 3-lithiation was preferred (91JOC4793).



4. Carbanion Formation on 2-Substituents in Pyridine

Although the utilization of unsaturated nitrogen heterocycles as ortho-lithiation directing groups is today very much dominated by the 4,4-dimethyl-2-oxazoline group (79OR1; 85T837), work with this substituent was preceded by the use of pyridine derivatives (79OR1). Thus, despite the facile nucleophilic attack often seen with pyridine derivatives, external metalation, at a carbon atom in a position (γ) with respect to the pyridine nitrogen, can occur in many cases. This is because the azomethine group represents one of the best ortho-lithiation directors known, mainly due to

TABLE XII
SYNTHESIS OF 3,4-DISUBSTITUTED PYRIDINES VIA DIRECTED METALATION
OF 3-SUBSTITUTED DERIVATIVES

Y	Metalation conditions	Electrophile	Yield (%)	Reference
F	<i>n</i> -BuLi/TMEDA/THF/ -40°C LDA/THF/ -78°C	Et ₃ CO I ₂ , TMSCl	50 50, 87	72CR(C)1535 ^a 80TL4137 ^a
F, 2,5,6-F ₃	<i>n</i> -BuLi/hexane/ -55°C	CO ₂	50	65JCS5045
F, 2-Cl	<i>n</i> -BuLi/THF/ -40°C	Me ₂ CO	70	72CR(C)1535
Cl	LDA/THF/ -78°C LDA/THF/ -60°C	Various	28–96 11–98	80TL4137 81JOM(216)139
Cl, 6-Cl	LDA/THF/ -78°C	TMSCl	“High”	92JOC1930
Cl, 2,6-Cl ₂	<i>n</i> -BuLi/Et ₂ O/ -70 → -20°C	D ₂ O, Me ₂ SO ₄	39, 48	74JOM(69)161
Br	LDA/THF/ -78°C LDA/THF/ -100°C	PhSSPh, DMF TMSCl ^c	61, 73 68 ^d	80TL4137; 83TL3291 ^b 91CB2119
CONEt ₂	LDA/Et ₂ O/ -45°C LDA/HMPT/THF/ -78 → 0°C	CONEt ₂ ^e CONEt ₂ ^e	68 90	86JCR(M)401, 86JCR(S)18 ^f 88S388
CONEt ₂ , 2-Br	LDA/THF/ -78°C	CICONEt ₂	80	91TL4883
CON(iPr) ₂	LDA/Et ₂ O/ -78°C LiTMP/DME/ -78°C	Various Various	20–73 53–98	86JCR(M)401, 86JCR(S)18 ^f 83TL2649; 87T5281
Ar- <i>o</i> -CON(iPr) ₂	LDA/THF/0°C → RT	CON(iPr) ₂ ^h	55	91JOC1683
Oxazoline ⁱ	LiTMP/THF/0°C	Various	9–80 ^j	78H133; 82JOC2633 ^k
NHCO- <i>t</i> -Bu	<i>n</i> -BuLi/TMEDA/Et ₂ O/ -10°C <i>n</i> -BuLi/THF/ -78 → 0°C	Various PhCONEt ₂	50–85 70	82S499; 89JHC105 ^l 87CJC1158 ^m
NHCO- <i>t</i> -Bu	<i>t</i> -BuLi/THF/ -78 → -20°C	Various	63–72	87CJC1158; 88JMC2136
OCH ₂ OMe	<i>t</i> -BuLi/Et ₂ O/ -78°C	D ₂ O, I(CH ₂) ₂ Cl	88, 90	82JOC2101; 83T2031
OSEM ⁿ	<i>t</i> -BuLi/Et ₂ O/ -78°C	Various	74–83	90TL4267
OCONEt ₂	<i>s</i> -BuLi/TMEDA/THF/ -78°C	Various	51–83	85JOC5436
OCSNEt ₂	LiTMP/THF/ -78°C	Various	82–91	92S112
SOPh	LDA/THF/ -78 → 0°C	TMSCl, PhCHO	80, 81	89TL7091
SO ₂ NR ₂ ^o	LDA/Et ₂ O/ -70°C	Various	42–95	83S822
SO ₂ NH- <i>t</i> -Bu	LDA/Et ₂ O/ -70°C	Ph ₂ CO, CO ₂	80, 80	92JHC61
CH(OLi)NRR ^p	<i>n</i> -BuLi/THF/ -42°C	Me ₃ SnCl	60	92JOC1593
Br, 6-OMe	LDA/THF/ -75°C	ArCHO	72	88JCS(P1)3085
OMe, 5-NHCO- <i>t</i> -Bu	<i>n</i> -BuLi/THF/ -25°C	Various	11–99	81JOC3564 ^q
OMe	MeLi/THF/ -23 → 0°C	MeI	67	90JOC69
2-CH(OLi)NRR ^r	<i>n</i> -BuLi/THF/ -42 → -23°C	MeI	82	90JOC69
CH(OLi)NRR ^p	<i>n</i> -BuLi/THF/ -42°C	MeI	65 ^s	90JOC69
2-OMe				
CH(OLi)NRR ^p				
6-OMe				

^a See also 83T2009.^b See also 82T3035.^c *In situ* reaction conditions.^d Crude material also contained 9% of 2-substituted isomer.^e Intermolecular mono-condensation.^f See also 80TL4739 and 83TL2649.

TABLE XII (Continued)

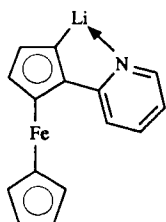
^k Intermolecular/intramolecular bis-condensation.
^h Intramolecular condensation.
ⁱ 4,4-Dimethyl-2-oxazoline.
^j The 80% yield represents the ethyl product from addition of MeI ($\text{ArLi} \rightarrow \text{ArCH}_3 \rightarrow \text{ArCH}_2\text{Li} \rightarrow \text{ArCH}_2\text{CH}_3$).
^k See also 91JCS(P1)3165.
^l See also 88JOC2740 and 90JCS(P1)2611.
^m See also 83JOC3401 and 90JOC4744.
ⁿ 2-(Trimethylsilyl)ethoxymethoxy.
^o NR_2 = piperidinyl.
^p NRR' = $\text{N}(\text{Me})\text{CH}_2\text{CH}_2\text{NMe}_2$.
^q See also 82CPB1257.
^r NR_2 = <i>N</i> -methylpiperazinyl.
^s Trace other isomer also obtained.

its good ligand properties and strong electron-withdrawing effect (79OR1). Examples of successful side-chain metalation include the 2'-lithioferrocenylpyridine **104** [67TL1483; 68JCS(C)656; 71JCS(C)3341], the (3'-lithio-2-thienyl)pyridine **105** (73TL4039; 83CB992, 83T3593), its furyl analog **106** (83T3593), and the vinyl sulfoxide **107** (78CL517).

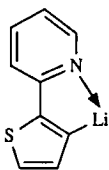
With the thiophene and furan derivatives, the site of metalation is highly dependent upon the reaction conditions, with the thermodynamic product being the one derived via metalation adjacent to the sulfur or oxygen heteroatom (α -metalation). Only under conditions that favor prior coordination of the lithium base with the pyridine nitrogen does directed metalation give rise to the γ -lithio derivatives. Aspects of this type of competitive metalation have been discussed elsewhere (79OR1; 83T3593). The lithiations of a number of other pyridine derivatives have also been investigated, including ring-fused compounds (79OR1; 83CB992), and the use of a 2-pyridyl group to direct metalation to the 3-position of indoles was mentioned in Section II,A,4.

5. Quinolines: Carbanions in Pyridine Ring

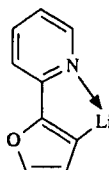
The situation regarding carbanionic derivatives of quinoline is analogous to that seen with pyridine, and all three possible carbanion types can be prepared, either by halogen-metal exchange reactions or by direct metalation of suitably substituted derivatives. The unsubstituted 2-, 3-, and 4-lithioquinolines have all been prepared and are readily available by lithium exchange with the analogous bromides [40JA446; 57JOC565;



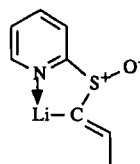
104



105



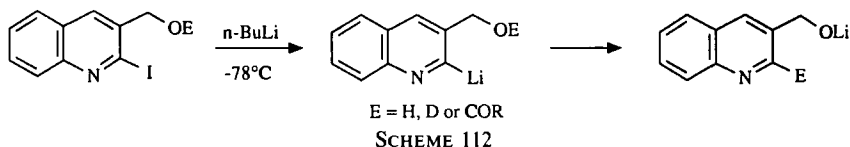
106



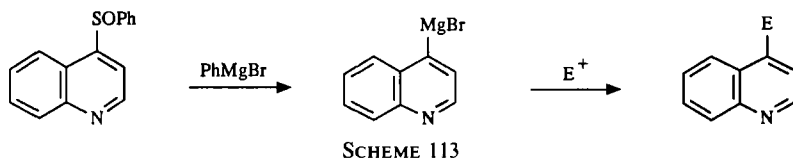
107

58JOC1584; 84H(22)2471]. The exchange of a 2-iodo atom for lithium is particularly facile, and it has even been claimed to occur in preference to deprotonation of adjacent hydroxyl groups, or nucleophilic addition to ester groups, as was shown by the isolation of 2-derivatized products on treatment of 2-iodo-3-hydroxymethylquinoline derivatives with *n*-BuLi (Scheme 112) (85CC1368; 90JA4431). However, this result has been contested in the case of the hydroxy or deuterioxy groups (91JA7984).

Magnesium derivatives are less common than with pyridine, although

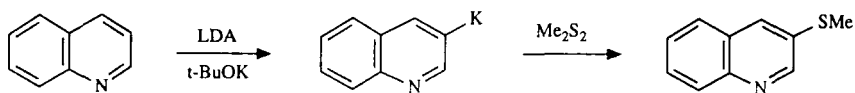


all three trimethylsilyl derivatives have been prepared in moderate yield using an *in situ* Grignard procedure [77JOM(136)323; 79S841]. The 4-quinolyl Grignard reagent has also been prepared by displacement of a 4-phenylsulfinyl group with PhMgBr (Scheme 113) (86TL3899). Subsequent reaction with a variety of carbonyl compounds occurred in moderate to good yield (86TL3899).



Attempted direct metalation of quinoline, with LDA at -70°C in ether, resulted only in the formation of 2,2'-diquinolyl, showing that although deprotonation occurred at the 2-position, further reaction with another

molecule of quinoline took place by addition to the azomethine double bond (74TL2373). In contrast, when quinoline was treated successively with LDA-*t*-BuOK and then dimethyl disulfide in THF-hexane at -60°C , 3-methylthioquinoline was obtained, showing that metalation had occurred at the 3-position (Scheme 114) (84CC257). Unfortunately, attempts at extending this result to other electrophiles were unsuccessful.

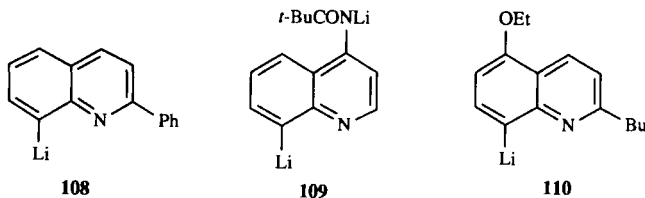


SCHEME 114

As with pyridine, the directed metalation of quinoline derivatives is a facile process [91AHC(52)187], and the lithiation of 2-ethoxyquinoline in the 3-position was reported as early as 1951, although in quite low yield (51JA32). However, better results have been achieved since that time, and a number of quinoline derivatives have now been successfully lithiated and derivatized, often in very good yield (Table XIII).

6. Quinolines: Carbanions in Benzene Ring

Although the metalation of heteroaromatic rings fused to rings bearing sp^2 pyridine-like nitrogen is normally quite facile (e.g., see Sections II.A,3 and II.E,6), the same is not true for carbocyclic rings. The direct lithiation of 2-phenyl-, 4-pivalamido-, and 2-butyl-5-ethoxyquinoline has been reported to give the 8-lithio derivatives **108**, **109**, and **110** [54OR258; 88JOM(354)273; 91AHC(52)187], presumably as a result of coordination to the quinoline nitrogen, but apart from that there are no reports on the direct metalation of quinolines at any other carbocyclic ring position.



However, lithiation at all carbocyclic positions can be achieved using directed metalation [91AHC(52)187], and both fluoro- and dimethylcarbamate derivatives have been successfully derivatized by this procedure [79JOM(171)273; 87JOM(336)1] (Table XIV).

TABLE XIII
 SYNTHESIS OF SUBSTITUTED QUINOLINES VIA DIRECTED METALATION

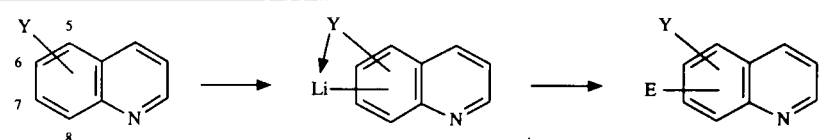
Y	Metalation conditions	Position	Electrophile	Yield (%)	Reference
2-F	LDA/HMPT/THF/ -60°C	3	TMSCl	58	79JOM(171)273
	LDA/THF/ -75°C	3	PhCHO	92	89JHC1589
2-Cl	LDA/THF/ -75°C	3	Various	45-85	89JHC1589
2-NHCO- <i>t</i> -Bu	3 <i>n</i> -BuLi/Et ₂ O/0°C	3	Various	11-95	86S670 ^d
2-OEt	<i>n</i> -BuLi/Et ₂ O/RT	3	CO ₂ , EO ^b	6.5, 4	51JA32; 71T1351 ^c
2-OCOR ₂ ^d	LDA/THF/ -78°C	3	CONR ₂ ^c	90	88CJC1135
2-OCONEt ₂	<i>s</i> -BuLi/TMEDA/THF/ -105°C	3	D ₂ O, RCHO	80, 28-30 ^f	88CJC1135 ^g
3-F	LDA/HMPT/THF/ -60°C	4	TMSCl	66	79JOM(171)273
3-Cl	LDA/THF/ -75°C	4	TMSCl	55	89JHC1589
3-OCOMe ₂	LDA/THF/ -78°C	4	ArCHO	50-95 ^h	87JHC1487 ⁱ
3-OCOR ₂ ^d	LDA/THF/ -78°C	4	Various	25-90	88CJC1135 ^g
3-NHCONMe ₂	LDA/THF/ -78°C	2	TMSCl	77	88JOM(354)273
4-Cl	LDA/THF/ -75°C	3	TMSCl	70	89JHC1589
4-OCOMe ₂	LDA/THF/ -78°C	3	CONMe ₂ ^c	80	88CJC1135
4-OCONEt ₂	LDA/THF/ -78°C	3	Various	43-95	88CJC1135 ^g
2,4-(OMe) ₂	<i>n</i> -BuLi/Et ₂ O/0°C	3	EO ^b , DMF	66, 94	71T1351; 79S903 ^j
	<i>n</i> -BuLi/THF/RT	3	RBr ^k	81 ^l	73JCS(P)194

^a See also 88JOM(354)273.^b EO = ethylene oxide (oxirane).^c See also 67CI(L)831.^d R = Me or Et.^e Anionic Fries rearrangement.^f Includes rearrangement products (19-24% overall yield) with aldehyde electrophiles.^g See also 88JHC1053.^h Products were 4-(dimethylaminomethyl)-3-hydroxyquinolines.ⁱ See also 88CJC1135.^j See also references in 83S957 and 87MI2.^k R = 3,3-dimethylallyl.^l Accompanied by 17% of the analogous 2-quinolone.

The preference for 8-metalation, seen with the 2-phenyl-, 4-pivalamido-, and 2-butyl-5-ethoxyquinolines, is continued, as shown by the absence of any 6-substituted products from the directed lithiation of 7-substituted derivatives. This type of preference is not seen with 6-substituted compounds, however, and a mixture of the 5,6,7-trisubstituted, and both possible disubstituted products, was obtained on treatment of the lithio derivative of the 6-carbamate with TMSCl at -78°C [78JOM(336)1].

Halogen-metal exchange reactions in the carbocyclic rings of quinolines have also successfully been achieved, and all four possible types of lithio

TABLE XIV
SYNTHESIS OF QUINOLINES SUBSTITUTED IN THE CARBOCYCLIC RING
VIA DIRECTED METALATION



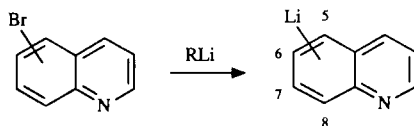
Y	Metalation conditions	Position	Electrophile	Yield (%)	Reference
5-F	LDA/HMPT/THF/ -60°C	6	TMSCl	30	79JOM(171)273
5-OCONMe ₂	LDA/THF/ -78 → 0°C	6	CONMe ₂ ^a	100	87JOM(336)1
	LDA/THF/ -78°C	6	TMSCl	70	87JOM(336)1
6-F	LDA/HMPT/THF/ -60°C	5	TMSCl	65 ^b	79JOM(171)273
6-OCONMe ₂	LDA/THF/0°C	7	CONMe ₂ ^a	80	87JOM(336)1
	LDA/THF/ -78°C	— ^c	TMSCl	— ^c	87JOM(336)1
7-F	LDA/HMPT/THF/ -60°C	8	TMSCl	30	79JOM(171)273
7-OCONMe ₂	LDA/THF/ -78 → -40°C	8	CONMe ₂ ^a	60	87JOM(336)1
	LDA/THF/ -78°C	8	MeOD, TMSCl	100, 90	87JOM(336)1
8-OCONMe ₂	LDA/THF/ -78 → 20°C	7	CONMe ₂ ^a	50	87JOM(336)1
	LDA/THF/ -60°C	7	TMSCl	40	87JOM(336)1

^a Anionic Fries rearrangement; see 87JOC1935.

^b 10% of 7-substituted product also obtained.

^c A mixture of 5,6-, 6,7-, and 5,6,7-trisubstituted products was obtained in the ratio 2 : 2 : 1.

derivative have been prepared from the analogous bromides (Scheme 115) [69JHC243, 80JOC1514; 87JOM(336)1; 89JMC1936].

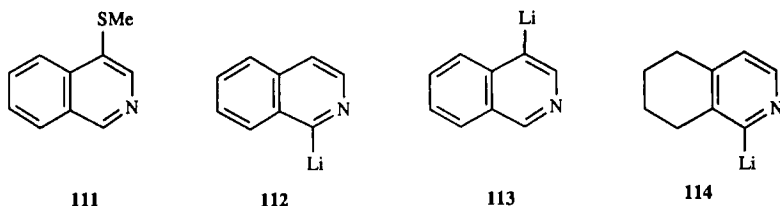


SCHEME 115

7. Isoquinolines

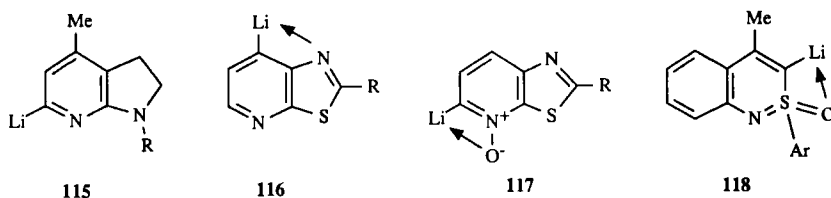
The situation with isoquinoline in many respects is similar to that seen with quinoline, although as yet there are no reports of the directed lithiation of substituted derivatives. 1,1'-Diisoquinolyl was obtained from the reaction of isoquinoline with LDA, showing that deprotonation occurred at the 1-position (74TL2373), whereas with LDA/*t*-BuOK and dimethyldisulfide the 4-derivative **111** was obtained (84CC257). Again, as with quinoline,

attempts to extend this result to other electrophiles were unsuccessful. Isoquinolyl carbanions have been successfully prepared by the use of halogen-metal exchange reactions, however, and both 1- and 4-lithioisoquinoline **112** and **113** have been prepared from the analogous bromides (57JOC565; 69JHC243). 1-Lithio-5,6,7,8-tetrahydroisoquinoline **114** has similarly been prepared [49LA(564)161], but as yet there appear to be no reports of the formation of 3-lithioisoquinoline derivatives.



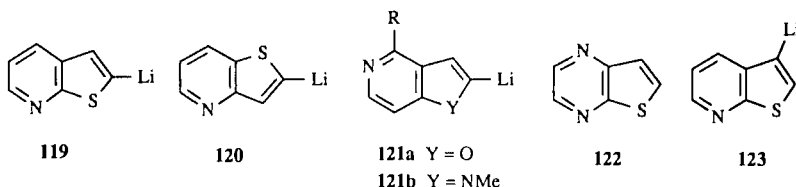
8. Other Bicyclic Pyridines

A number of other bicyclic pyridine derivatives have been converted to lithio derivatives, and examples are the dihydro-azaindoline derivative **115**, which was formed from the analogous chloride by treatment with lithium naphthalide (77KGS1527), and the thiazolopyridine derivative **116**, which was formed from the parent heterocycle by direct lithiation with LDA (89TL183). In contrast, when the analogous *N*-oxide was treated with *n*-BuLi, directed metalation occurred adjacent to the pyridine nitrogen to give the α -lithio derivative **117** (89TL183). Finally, the lithiated benzothiazine derivative **118** can be formed by a directed metalation involving the sulfoximine functionality (88TL5229).



There are several bicyclic compounds with five-membered heterocycles fused to pyridine rings, where metalation occurs in the smaller ring due to activation by the heteroatom. The ring-A lithiation of imidazopyridines and pyrimidines was discussed in Section II,E,6, but in addition, the α -lithio derivatives of thieno[2,3-*b*]pyridine **119** (74JHC355), thieno[3,2-*b*]pyridine **120** (84JHC785), and both furo and pyrrolo[3,2-*c*]pyridines **121a** and **121b** (83T1777) have all been prepared by direct lithiation using *n*-

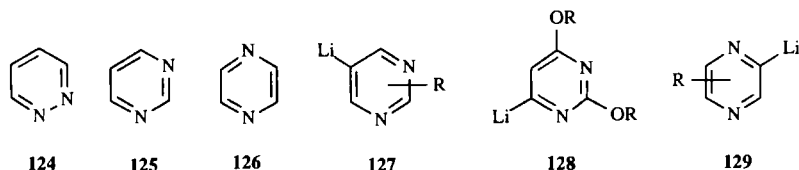
BuLi, *n*-BuLi/TMEDA, or *t*-BuLi. Success in the metalation of thieno[2,3-*b*]pyridine is highly dependent upon the reaction conditions, and thus although the lithio derivative **119** can be prepared using either methyllithium (69JOC347) or *n*-BuLi/TMEDA (74HC355), only addition to the azo-methine bond occurs with *n*-BuLi (69JOC347). Similarly, when lithiation of the more electron-deficient thieno[2,3-*b*]pyrazine **122** was attempted with *n*-BuLi, only nucleophilic addition to the six-membered ring was observed (80JHC1019). Halogen-metal exchange has also been used with these systems, as shown by formation of the β -lithio derivative **123** from the analogous bromide (74JHC355).



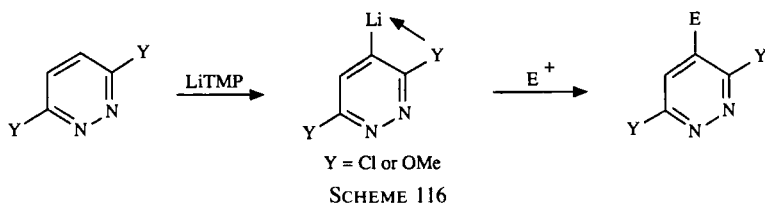
B. DIAZINES

1. Pyridazine, Pyrimidine, and Pyrazine

The three diazines pyridazine **124**, pyrimidine **125**, and pyrazine **126** are even more susceptible to nucleophilic addition than pyridine, and examples of carbanionic derivatives are therefore less prevalent, although a number of metalated species have now been prepared. Several 5-lithiated pyrimidines **127** have been synthesized via halogen-metal exchange reactions with the analogous bromides [84M11; 85JOC841; 88ACS(B)455, 88ACS(B)530, 88JOM(342)1; 89ACS684], and although this type of transformation has also been used to give 4-lithio derivatives **128** (56JA2136; 78JOC511; 85JOC841), attempts at extending the reaction to the 2-isomeric system were unsuccessful (65ACS1741). Iodine-lithium exchange has been used to give 2-lithio pyrazine derivatives **129** (65JHC209; 69JHC239; 92JMC295), but attempts to use chloro or bromo compounds have been unsuccessful. There do not appear to be any examples of halogen-metal exchange reactions having been performed with pyridazine.



The direct metalation of 5-methylpyrimidine and 5,5'-bipyrimidinyl in the 4-position has been reported with LDA in low yield [74TL2373; 75AG(E)713], but apart from that there are few other reports on the direct metalation of unactivated diazines. However, as with pyridine and quinoline, directed metalation can readily be achieved with all three of the diazine systems when the appropriate substituent groups are present [91AHC(52)187]. Thus, the direct lithiation of pyridazine in the 4-position has now been achieved with both the 3,6-dichloro and the 3,6-dimethoxy derivatives, using the nonnucleophilic lithium 2,2,6,6-tetramethylpiperidide (LiTMP) as base in THF at either -70 or -78°C (Scheme 116) [90JHC1377, 90JOC3410].



The directed metalation chemistry of pyrimidine is more extensive than that of pyridazine, and both 4- and 5-substituted derivatives can be prepared by this route (Table XV).

As with the β -metalation of pyridine (Table XI), the addition of a substituent containing a heteroatom at C-6 results in more efficient metalation at C-5, whereas the presence of a 2-substituent also tends to increase the reaction efficiency, presumably by cutting down on alternative modes of reaction. Nonnucleophilic LiTMP is the most utilized base system, followed by LDA, although *n*-BuLi has also been used, but only in those cases where the 2-position was substituted.

Examples of the 3-lithiation of both 2- and 2,6-disubstituted chloro- and methoxypyrazines, as well as 2-thiomethylpyrazine are known (88S881; 90JOC3410; 91JHC765, 91JOM(412)301] (Scheme 117). As with pyridazine, LiTMP has so far been the only base employed, and this same base system has also recently been used for the directed metalation of pyrazine 1-oxides in the 2-position (91H735).

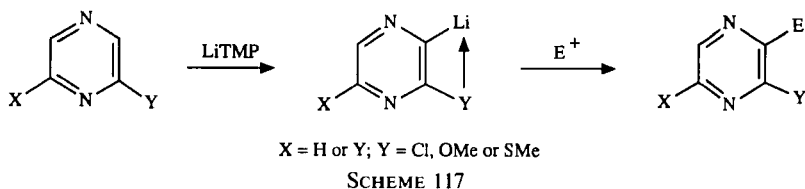


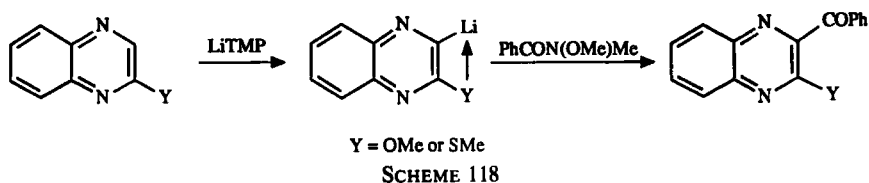
TABLE XV
SYNTHESIS OF SUBSTITUTED PYRIMIDINES VIA DIRECTED METALATION

Substituents	Metalation conditions	Position	Electrophile	Yield (%)	Reference
5-Br	LDA/Et ₂ O/ -10°C	4	ArCOR ^a	25-40	79JOC2081
5-OMe	LiTMP/THF/ -78°C	4	Various	47-49 ^b	90JOC3410
4-OMe	LiTMP/Et ₂ O/ -70°C	5	TMSCl	5	90JHC1831 ^c
4-O(CH ₂) ₂ OMe	LiTMP/Et ₂ O/0°C	5	TMSCl, PhCHO	13, 55	90JHC1831 ^c
2,4-Cl ₂	LiTMP/THF/Et ₂ O/ -100°C	5	MeCHO	11	90JHC1377
	LiTMP/THF/HMPA/ -70°C	5	D ₂ O, MeCHO	43, 19	90JHC1377
	LDA/THF/ -80°C	5	TMSCl, PhCHO	6, 38	91JOC4793
2-Cl, 4-OMe	LiTMP/Et ₂ O/0°C	5	TMSCl, PhCHO	30, 35	90JHC1831 ^c
2-Cl, 4-OR ^d	LiTMP/Et ₂ O/0°C	5	TMSCl	15	90JHC1831 ^c
2,4-(OMe) ₂	LiTMP/Et ₂ O/0°C	5	Various	4-65	90JHC1831 ^c
	LiTMP/THF/ -78°C	5	Various	68-98 ^b	90JOC3410
2,4-(OR) ₂ ^d	LiTMP/Et ₂ O/0°C	5	TMSCl	18	90JHC1831 ^c
4,6-Cl ₂	LDA/THF/ -80°C	5	TMSCl, PhCHO	44, 60	91JOC4793 ^e
4,6-(OMe) ₂	LiTMP/THF/ -78°C	5	Various	75-97 ^f	90JOC3410
2,4,6-Cl ₃	<i>n</i> -BuLi/THF/ -80°C	5	PhCHO	82	91JOC4793
	LDA/THF/ -80°C	5	TMSCl, PhCHO	67, 84	91JOC4793
4-Cl, 2,6-(OMe) ₂	LiTMP/THF/ -25°C	5	Various	62-90	91JHC283
6-Cl, 2,4-(OMe) ₂	<i>n</i> -BuLi/THF/ -70°C	5	Me ₃ SiCl ^g	56, 42	88JOM(342)1
2,4,6-(OMe) ₃	LiTMP/THF/ -78°C	5	Various	91-99 ^f	90JOC3410

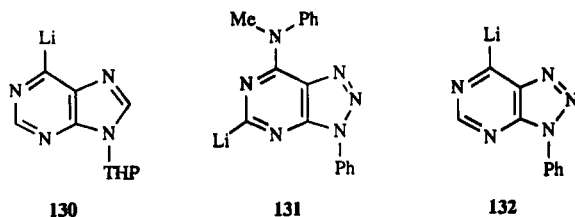
^a Includes R = H.^b Complex mixture of products when PhCOCl used as electrophile.^c Preliminary communication 87H(26)585.^d R = CH₂CH₂OMe.^e See also 86S886.^f Includes successful reaction with PhCOCl.^g M = Si and Sn.

2. Quinoxaline and Other Bicyclic Diazines

Very little attention has been given to the metalation of the quinoxaline system, although lithiation of the 2-methoxy and 2-methylthio derivatives has recently been achieved (Scheme 118) (91JHC765). Reaction with *N*-methoxy-*N*-methylbenzamide occurred at -78°C to give the analogous phenyl ketones in moderate yield. Highly colored insoluble solids were also produced, and these were the sole products when metalation of 2-chloroquinoxaline was attempted.

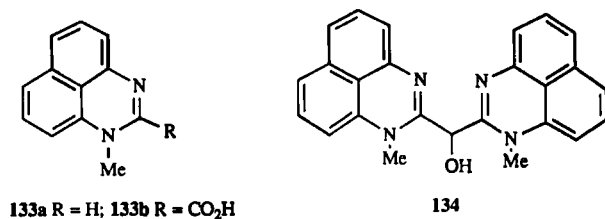


As with their monocyclic analogs, lithiated derivatives of bicyclic diazines can be prepared by halogen-metal exchange at low temperature, and examples include the 6-lithiopurine **130** (79JOC4612), and the 5- and 7-lithio-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines **131** and **132** (91CPB2793, 91CPB3037).



3. Perimidines

Investigations on the lithiation of *N*-substituted perimidines have so far been restricted to the *N*-methyl derivative **133a**, which has been found to undergo addition across the imine double bond with alkylolithiums (75KGS1682; 81RCR816), and radical anion formation with LDA (88AJC139). Some C-2 lithiation does occur, however, as is indicated by the formation of an 8% yield of the 2-carboxylic acid **133b** after reaction with *n*-BuLi and carbon dioxide (75KGS1682; 81RCR816), and a 19% yield of the bis(2-perimidinyl) carbinol **134**, which was isolated after treatment



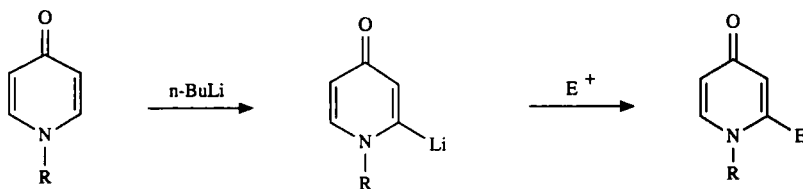
with LDA and DMF (88AJC139). The alcohol product is presumed to arise by reaction of the initially formed 2-aldehyde with a further equivalent of the 2-lithio anion.

As yet no one has investigated the use of complexing groups on the nitrogen atom, as a means of stabilizing the 2-lithio species, although this is obviously an area worthy of investigation in light of the interest being shown in 2-substituted pyrimidine derivatives as experimental anti-tumor agents (87JMC2081; 90MI3).

C. PYRIDONES AND PYRIMIDINONES

1. Pyridones

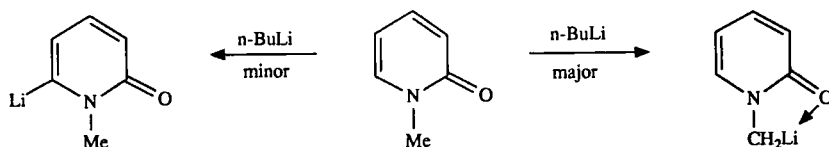
The lithiation of 1-methyl-4-pyridone with *n*-BuLi at -78°C proceeds smoothly at the C-2 position, and after reaction with electrophiles a variety of 2-substituted derivatives can be obtained (Scheme 119) [85CC1021;



SCHEME 119

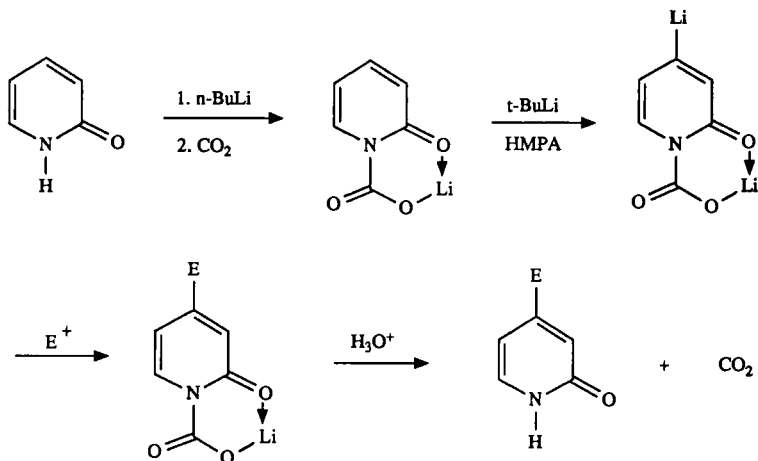
88JCS(P1)1]. Removable N-substituents have also been investigated, including methoxymethyl, benzyloxymethyl, and SEM [88JCS(P1)1], but, with the exception of deuteration, only poor product yields were obtained from reaction with electrophiles.

Attempts to extend this process to the related 2-pyridone system have been less successful, with only a small proportion of C-6 lithiation being observed with 1-methyl-2-pyridone [85CC1021; 88JCS(P1)1]. In fact, the major mode of reaction involves lithiation of the exocyclic methyl group, to give a carbanionic species that is dipole-stabilized by the heterocyclic amide group (Scheme 120) (83MI1).



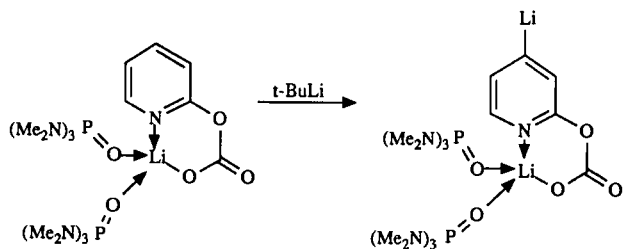
SCHEME 120

So far the only removable N-substituent to have been investigated with this system is the lithium carboxylate group, but instead of lithiation at the 6-position as expected, C-4 lithiation was observed (Scheme 121) (87T2343). Reaction with a variety of electrophiles occurred in moderate to good yield.



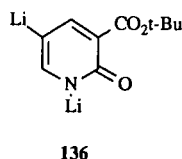
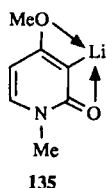
SCHEME 121

Reasons for reaction at C-4 rather than C-6 are not clear, but one possibility is that reaction actually occurs via the carboxy-pyridine form. If that is so, then both steric bulk around the 6-position and the greater acidity of the 4-proton could favor deprotonation at C-4 (Scheme 122).



SCHEME 122

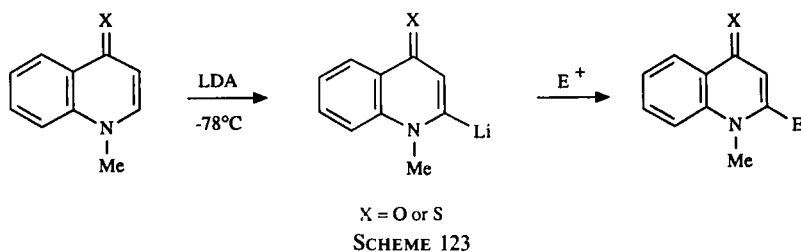
Metalation at the β -position of 2-pyridones has also been achieved, and thus the lithiation of 4-methoxy-1-methyl-2-pyridone occurred exclusively at the 3-position to give **135** [92JCS(P1)67], whereas halogen-metal exchange on the analogous bromide was used to generate the 5-lithio deriva-



tive **136** (84JHC1705). Protection of the pyridone nitrogen was not necessary in this case, with reaction occurring via the *C,N*-dianion.

2. Quinolones and Quinolinethiones

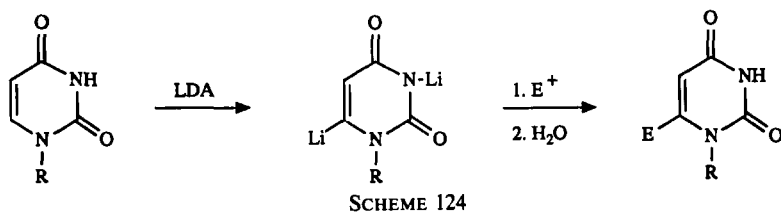
Attempted lithiation of *N*-methyl-4-quinolone with alkyllithiums was unsuccessful, due to nucleophilic addition at the 2-position, but efficient 2-lithiation could be achieved by reverse addition of the quinolone to excess LDA at -78°C [92JCS(P1)351]. The excess of base was found necessary in order to minimize dimer formation caused by reaction of the lithio species with nonlithiated starting material. Interestingly, the same reaction sequence was found to be successful with the analogous quinoline-4-thione, and both lithio species were able to be reacted with a variety of electrophiles to give a number of different 2-substituted derivatives (Scheme 123).



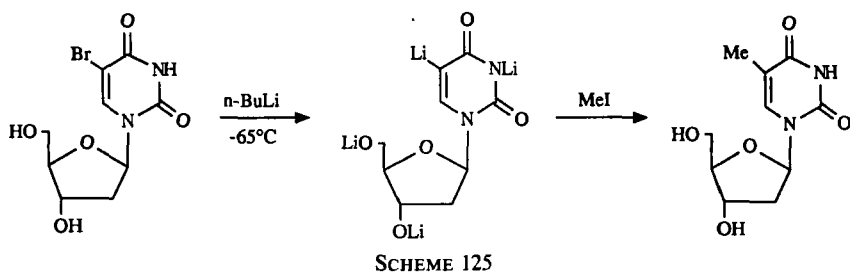
3. Pyrimidinones and Pyrimidinediones

In addition to deprotonation of the NH group, α -lithiation at the 6-position of uracils and related uridines and thymidines can be achieved with *n*-BuLi or LDA, provided that the hydroxyl groups of the ribose or deoxyribose sugar portion are suitably protected in the case of the nucleoside examples (73BSF2715; 81CPB3565; 82T2635; 83CPB2164; 84TL3325; 85T861; 89MI1). Nonnucleoside derivatives of uracil and thymine, which are of interest as anti-HIV agents, have recently been metalated in a similar

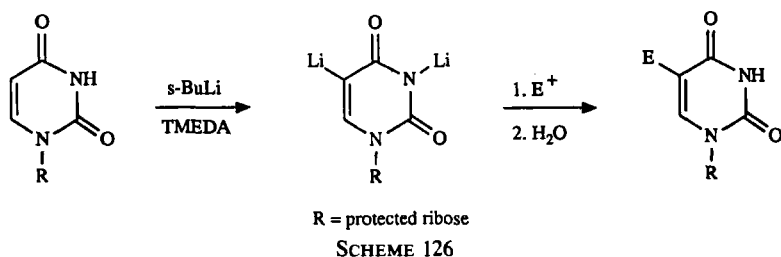
fashion (Scheme 124) (89JMC2507; 91JMC349, 91JMC1394, 91MI4, 91YGK1142; 92JMC337).



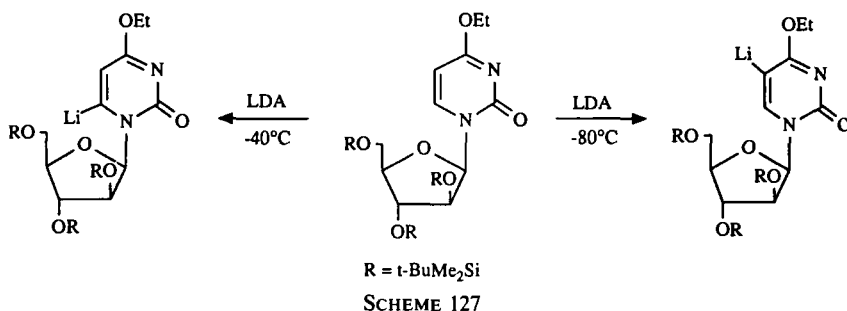
If the 6-position of uridine nucleosides is blocked, then lithiation can occur at the 5-position (89MI1), and similar metalation of a 6-unsubstituted derivative has been achieved using halogen-metal exchange (Scheme 125) (59T225).



However, the tetralithiated species proved to be insoluble in THF, and although improved solubility can be achieved by protection of the hydroxyl groups (85JOC841), the halogen-metal exchange route has mainly been superseded by direct lithiation procedures (89MI1). Thus, unlike the situation that prevails with LDA, where α -lithiation occurs in the 6-position of protected uridine nucleosides, lithiation of similar compounds with *sec*-butyllithium and TMEDA occurs in the adjacent 5-position, provided that the ribose or deoxyribose hydroxyl groups are protected by bulky groups such as *tert*-butyldimethylsilyl (Scheme 126) (87TL87; 89MI1, 89TL2057).



In contrast to the above situation, the 5-metalation of a 4-ethoxy- β -D-arabinofuranosyl derivative has actually been achieved using LDA, although the reaction was found to be very dependent upon the reaction conditions, with exclusive 6-lithiation being observed at higher temperatures (Scheme 127) (90TL1295).



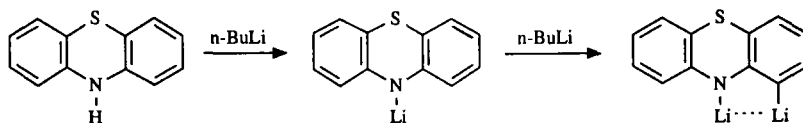
Metalation at the 5-position is dependent upon steric hindrance of the 6-position by the adjacent β -2'-*tert*-butyldimethylsilyloxy group, since exclusive 6-metalation was observed with the isomeric ribofuranoside where the 2'-substituent was in the α -position (90TL1295).

D. PHENOTHIAZINES AND PHENOXAZINES IN THE BENZO RING

1. *N*-Unsubstituted Phenothiazines and Phenoxazines

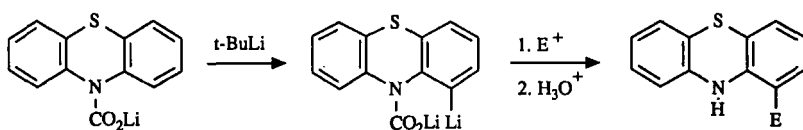
Phenothiazine efficiently undergoes direct lithiation at the C-1 position on treatment with *n*-BuLi (79OR1; 88MI1, 88MI4). As with all other N—H-containing heterocycles, initial ionization occurs on nitrogen, but instead of reaction stopping at that point, a directed metalation involving the N-anion, or its lithium counter-ion, then occurs to give the 1,10-dilithio species (Scheme 128).

Reaction at the C-1 position has been achieved with a variety of electrophiles including carbon dioxide (44JA625), lithium carboxylates (60BSF1049), dialkylamides (82JHC433), and dihaloalkanes (83SC467).



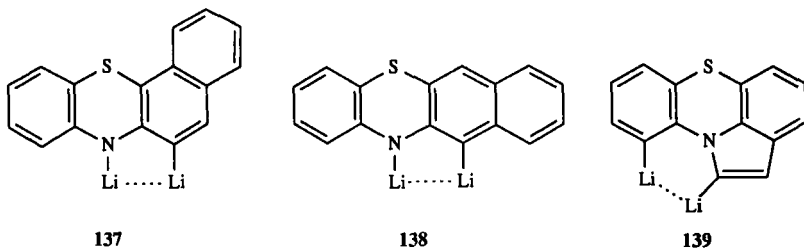
SCHEME 128

However, reaction at the nitrogen center is seen with other electrophiles such as acetyl chloride (82JHC433) and trimethylsilylchloride (85H357). Protection of the nitrogen with alkyl or aryl substituents results in reaction at C-4 rather than at C-1 [44JA1214; 60BSF1049; 64JOM(2)304], and although metalation at C-1 can be achieved with some *N*-acyl derivatives, using LDA or LiTMP at -78°C , the lithiated species then undergo a rapid intramolecular $\text{N} \rightarrow \text{C}$ migration to give the analogous 1-acyl derivatives (86TL1959). Fortunately, however, no such migration is observed with the *N*-carboxylate derivative, presumably due to repulsion by the negative charge, and 1-substituted products are able to be obtained in very good yield (Scheme 129) (88S215). At present this is the only method available for producing 1-substituted phenothiazines, without contamination by *N*-substituted byproducts.



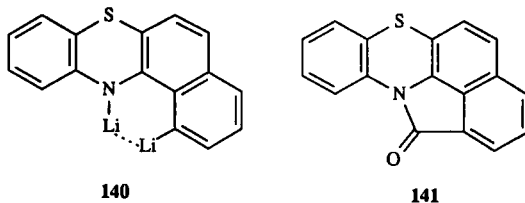
SCHEME 129

The direct lithiation of 7*H*-benzo[*c*]- and 12*H*-benzo[*b*]phenothiazines, which have two different sites adjacent to the nitrogen available for reaction, has also been investigated, but in each case it has been shown that reaction occurred exclusively on the (more acidic) naphthyl carbon to give **137** and **138**, respectively [60JOC2238; 64JOM(2)188]. However, reaction is not as clean with the fused pyrrolo[3,2,1-*kl*]phenothiazine, which lacks the free nitrogen capable of directing metalation to the β -position. A mixture of both α - and β -lithiated derivatives is obtained on reaction with *n*-BuLi or *s*-BuLi, whereas with an excess of base, cooperative lithiation at both sites is observed, resulting in the isolation of the dilithio derivative **139** (83H33).

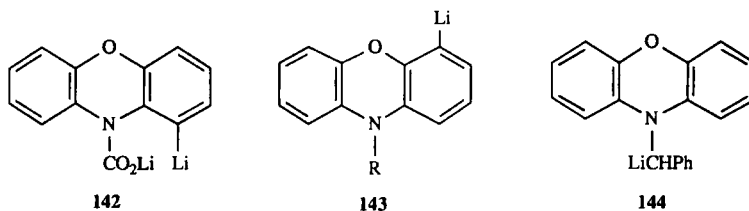


Directed metalation by the *N*-anion of phenothiazines is not confined to β -lithiation, and it is even more facile when a γ -proton is involved. Thus,

benzo[*a*]phenothiazine undergoes directed lithiation at the adjacent benzo position (60JOC1189; 62JOC4421), even though a vacant β -position is also available. Reaction of the 1,12-dilithio derivative **140** with CO₂ gives a mixture of the expected 1-carboxylic acid and the analogous lactam **141**, formed by reaction at both anionic centers.

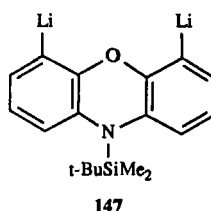
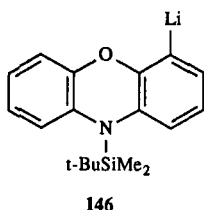
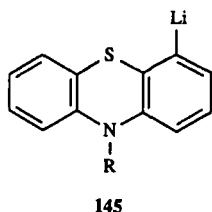


The metalation of phenoxazine has also been investigated, but in contrast to phenothiazine, direct lithiation at C-1 can only be achieved in very low yield (58JA2195; 68JMC807). Fortunately, however, the carboxylate protection method is just as efficient as that with phenothiazine, and the 1-lithio derivative **142** can readily be obtained by treatment with *t*-BuLi [87H(26)3135]. This result is the stark contrast to that seen with *N*-alkyl or *N*-benzyl phenoxazines, where reaction occurs predominantly at C-4 or on the exocyclic methylene group, to give **143** and **144**, respectively (58JA2195; 89JOC2159).



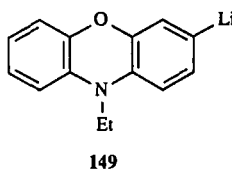
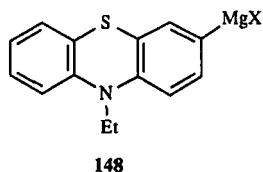
2. *N*-Substituted Phenothiazines and Phenoxazines

Although it has been reported that the lithiation of *N*-substituted phenoxazines and phenothiazines gives only the 4-lithio derivatives **143** and **145** [44JA1214; 58JA2195; 64JOM(2)304], more careful analysis of the reaction products has shown that both 1- and 4-lithiation occurs, but with the latter predominating (60BSF1049; 89JOC2159). Increasing the size of the *N*-substituent retards lithiation at the 1-position, and good yields of 4-substituted derivatives have been obtained via the 4-lithio-10-(*tert*-butyldimethylsilyl)phenoxazine **146** (89JOC2159). Dilithiation also occurs with excess base to give the 4,6-dilithio derivative **147**. In either case,



desilylation occurred readily with tetrabutylammonium fluoride after reaction with a variety of electrophiles, and good yields of 4- or 4,6-disubstituted phenoxazines were obtained (89JOC2159).

Halogen-metal exchange reactions provide the main route to 3-lithiated derivatives of phenothiazine and phenoxazine and examples of metalated compounds formed by the use of such exchange reactions include the 3-halomagnesium derivatives of 10-ethylphenothiazine **148** (44JA1214; 55JA3862) and the 3-lithium derivative of 10-ethylphenoxazine **149** (58JA2195).



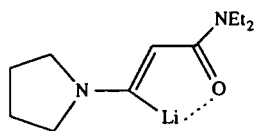
V. Nonaromatic Ring Systems

A. SATURATED RINGS

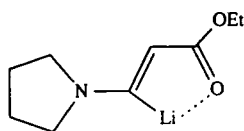
1. Carbanions α - to Nitrogen

Acyclic sp^2 (vinyl)-carbanions adjacent to sp^3 -nitrogen are fairly rare, and heterocyclic examples even more so, although some are known (84T2989). Thus the acrylamide and acrylate derivatives **150**, **151**, and **152** can be formed by deprotonation with t -BuLi at temperatures below -100°C , and once formed the amide **150** is stable up to room temperature [76AG(E)171; 78AG(E)204; 79TL4273].

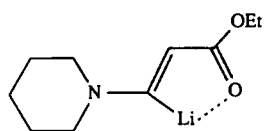
The nitrile **153** similarly can be formed below -105°C by a kinetically controlled deprotonation with LDA, but on warming above -100°C it readily rearranges to the thermodynamically more stable vinyllithium derivative **154** [77AG(E)853]. In contrast the morpholino derivative **155** is



150

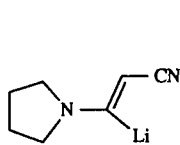


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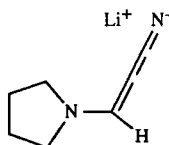


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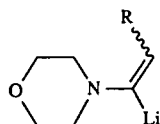
formed not by direct deprotonation, but by breakdown of the amidrazone **156** on treatment with 2.2 eq of *t*-BuLi at -78°C , followed by warming to 10°C (81CC1121).



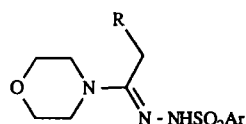
153



154

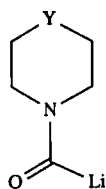


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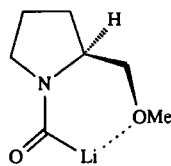
156

In addition to α -vinyl carbanions it is also possible to form α -acyl carbanions adjacent to heterocyclic nitrogen (85S253). Thus both *N*-formyl **157**, **158** and *N*-thioformyl **159**, **160** derivatives are known, and these can be formed by direct deprotonation of the formamides [76CB1309; 81AG(E)795], by carbonylation of the lithium amides with carbon monoxide [79AG(E)85; 83CC861; 88JOC408], and by transmetalation reactions involving tellurium species (90SC703).

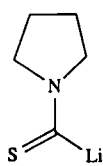


Y = CH₂ or O

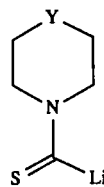
157



158



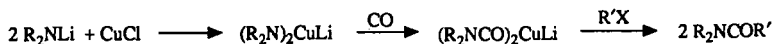
159



Y = CH₂, O or NMe

160

In the carbonylation reactions, further reaction of the acyl lithium compounds with carbon monoxide can occur, but clean reaction can be achieved if the lithium amide is first converted to a copper derivative (Scheme 130) (79JOC3734). In the case of morpholine, reaction with allyl bromide gave a 93% overall yield of the amide product.

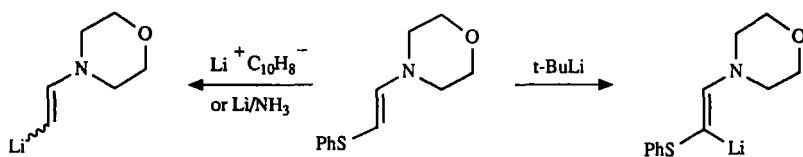


R_2N = morpholino

SCHEME 130

2. Carbanions β - to Nitrogen

The β -position of an enamine system is much more difficult to metalate than the α -position because of the higher electron density on the β -carbon, and so additional activation, or stronger base systems, are often required for efficient reaction. Thus, successful β -lithiation of the 3-(phenylthio)enamine of morpholine can be achieved because of the stabilizing effect of the sulfur atom, whereas reductive lithiation of the same species can be achieved with lithium naphthalenide or lithium in liquid ammonia (Scheme 131) [82JCR(M)621, 82JCR(S)48]. Similar β -lithioenam-



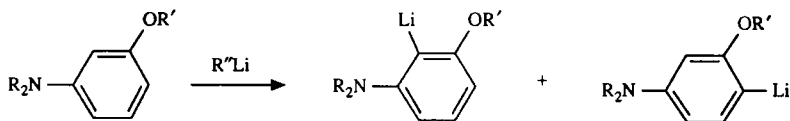
SCHEME 131

ines of morpholine are available much more readily via halogen-metal exchange reactions, however [70JOC1204; 81JOM(218)309; 82BSF(2)297; 83JCR(M)2101, 83JCR(S)222; 84T2989; 91S649].

The nitrogen atoms in *N,N*-disubstituted anilines are also poor β -directing groups because their lone-pair electrons are strongly engaged in the resonance of the π system, and are therefore not available for coordination with the lithiating reagent (79OR1). Metalated cyclic aniline derivatives are therefore not very common, although a number of 3'-substituted derivatives of *N*-phenylpyrrolidine, *N*-phenylpiperidine, and *N*-phenylmorpholine have been lithiated in order to investigate their site of lithiation (85JOC2690). In the case of the 3'-methoxy and 3'-methoxymethyl compounds, mixtures of 2'- and 4'-substituted derivatives were normally obtained (Scheme 132), but with a 3'-(diethylcarbamoyl)oxy group only 4'-substituted derivatives were observed.

3. Carbanions γ - to Nitrogen

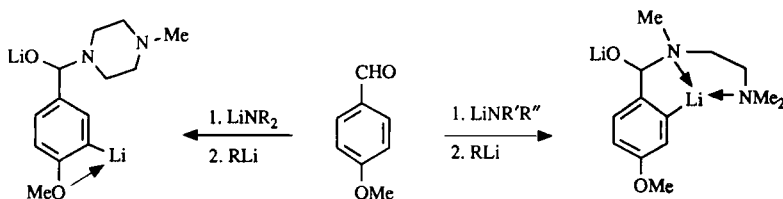
The external γ -metalation of nonfused azaheterocycles has received considerable attention in aromatic lithiation chemistry, although often



*R*₂N = pyrrolidino, piperidino or morpholino; *R'* = Me, CH₂OMe or CONEt₂

SCHEME 132

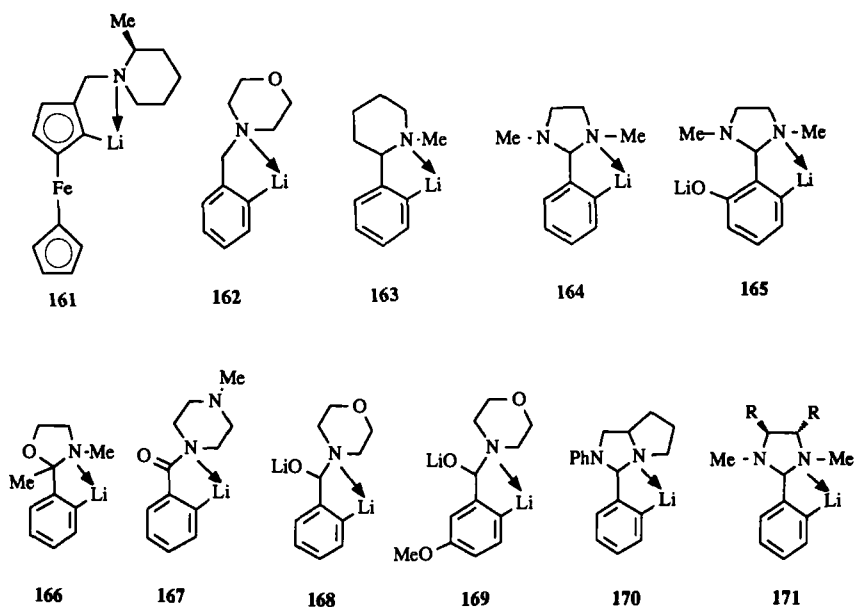
these metalations are merely cyclic examples of reactions that also occur with acyclic directing groups. However, there are cases where steric factors can result in a product substitution pattern different than that for acyclic directing groups. Thus, in the metalation of aldehydes via the intermediacy of their α -amino alkoxides, different products are often formed with *N*-methylpiperazine compared with the acyclic *N,N',N'*-trimethylethylenediamine (Scheme 133) (84JOC1078).



SCHEME 133

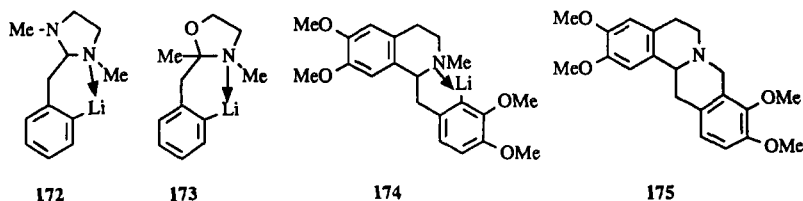
However, external γ -metalation of nonfused azaheterocycles is not confined to the directed aromatic lithiation area; there are heterocyclic systems that can be metalated in their own right. Examples of the different types of compound are the chiral ferrocene derivative **161** (70T5453, 70TL1771), *N*-benzylmorpholine **162** (71JMC1072), 2-phenyl-*N*-methylpiperidine **163** (79OR1), and the protected benzaldehyde derivative **164** (79JOC2004). In fact lithiation occurs in the latter system even in the presence of an *ortho*-hydroxy group to give the dianion derivative **165**. Subsequent hydrolysis gives 6-substituted salicylaldehydes in overall yields ranging from 10 to 95% (91MI8).

Acetophenone derivatives **166** (79OR1), as well as amide derivatives such as the *N*-benzoyl-*N'*-methylpiperazine **167** (86JOC3566), and other related benzamides have also been investigated (90CRV879). In addition, halogen-metal exchange has also been used to generate aromatic azaheterocyclic- γ -carbanions, with examples including the α -amino alkoxides **168** and **169** (81TL4213; 89JOC3730), and the chiral 2-phenylimidazolidines **170** and **171** (80CL17; 90TA287).



4. Carbanions δ - to Nitrogen

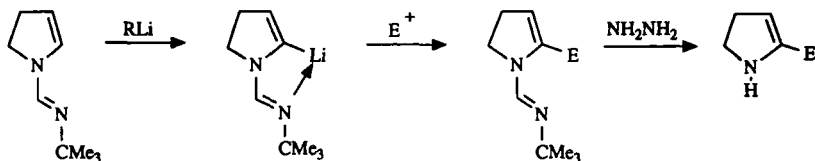
Examples of the direct δ -metalation of nonfused compounds containing heterocyclic sp^3 -nitrogen are quite limited, often because of competing side-reactions such as benzylic deprotonation. However, with the appropriate substitution pattern δ -metalation can occur even in those cases where benzylic deprotonation is a possibility. Examples of successful δ -lithiation include the imidazolidine **172** and 2-methyloxazolidine **173** (91G249), as well as the tetrahydroisoquinoline derivative **174** [69CI(L)621], although in this latter case subsequent steps resulted in only a 10% yield of the desired product **175**.



B. PARTIALLY SATURATED FIVE-MEMBERED RINGS

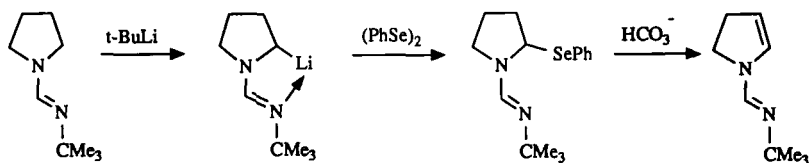
1. 2,3-Pyrrolines

The lithiation of 2,3-pyrrolines has received only moderate attention, but two different nitrogen protection systems have been found acceptable. Thus the *tert*-butylformamidine derivative metalates readily with either *n*- or *t*-butyllithium, and after reaction with a variety of electrophiles the formamidine group can be removed with hydrazine to give 2-substituted 2,3-pyrrolines in very good yield (Scheme 134) (85JOC1019).



SCHEME 134

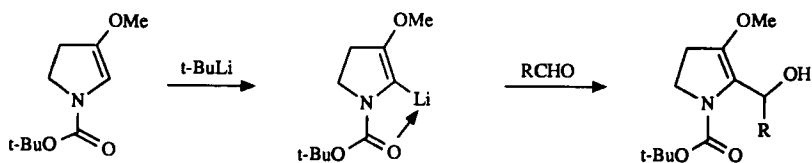
Interestingly, the protected pyrroline starting material is obtained from the analogous pyrrolidine via the intermediacy of the dipole-stabilized sp^3 -carbanion and diphenylselenide derivatives (85JOC1019) (Scheme 135).



SCHEME 135

The greater acidity of the α -protons of pyrroline compared to the pyrrolidine is demonstrated by the fact that whereas *n*-butyllithium is strong enough to form the unsaturated (sp^2) carbanion, *t*-butyllithium is necessary for the saturated (sp^3) system.

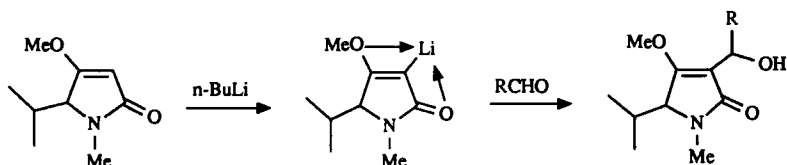
In addition to the formamidine system, the *tert*-butylcarbamate of the 3-methoxy derivative has also been lithiated and trapped with aldehydes at C-2, in what overall represents the formal reaction of a 3-pyrrolidone 2-enolate (Scheme 136) (90CC831). 3-Pyrrolidone normally forms the 4-enolate, so the use of the pyrroline route provides a solution to this problem, but the chemistry was found to suffer from a number of other problems, including an inability to react with alkyl halides, and the method



SCHEME 136

has since been superseded by an alternative process involving double deprotonation of a β -ketoester (90CC1047).

Finally, 1,5-disubstituted-4-methoxypyrrolidones undergo directed metalation adjacent to both the methoxy and the carbonyl groups, and after reaction with aldehydes a variety of alcohol derivatives were obtained (Scheme 137) (83TL4751).

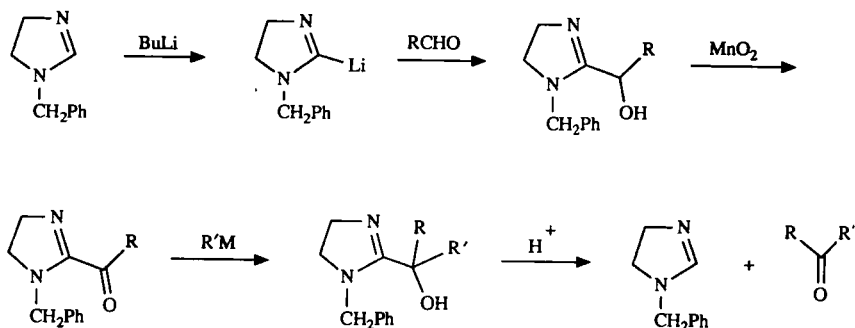


SCHEME 137

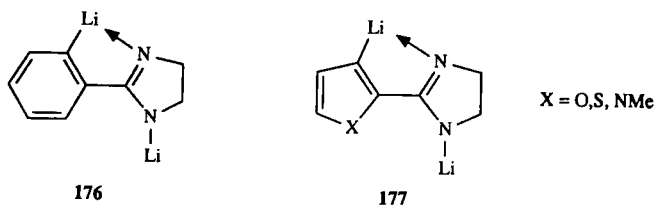
2. Imidazolines

The metalation chemistry of the imidazoline system has received attention only recently, with the lithiation of 1-benzyl-2-imidazoline being found to occur at the 2-position (90TL1767). Although the reactivity of the lithiated species with alkyl halides was poor, better results were achieved with disulfide and carbonyl electrophiles (90TL1767, 90TL1771). The products formed by reaction with ketones were found to be unstable with respect to fragmentation, and this result was utilized to provide a new route for the synthesis of unsymmetric ketones (Scheme 138).

As previously found with benzimidazole [78CI(L)582], the imidazoline group is a strong director for the *ortho*-metalation of 2-substituent groups, with both 2-phenyl **176** and 2-heteroaryl **177** lithiated derivatives having been prepared (82JOC5177; 91SC85; 91T9901). Reaction occurs readily despite the presence of a negative charge on the sp^3 -nitrogen, and the selectivity achieved in the case of 3-metalation of the *N*-methylpyrrole derivative was superior to that seen with any other directing group (91T9901).

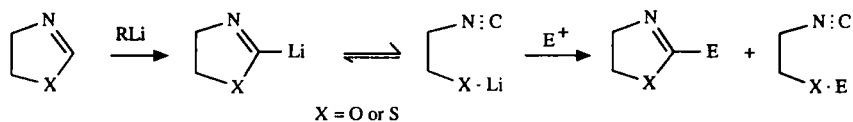


SCHEME 138



3. Oxazolines and Thiazolines

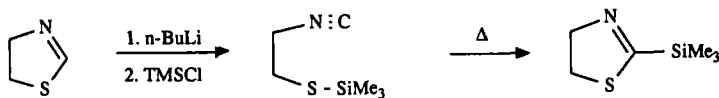
Oxazolines and thiazolines are lithiated at the 2-position to give species that, like oxazole (Section III,B,1), are in equilibrium with ring-opened forms [70JA6676; 90H(31)1213]. Subsequent reaction with electrophiles can occur via either form (Scheme 139), with soft electrophiles (e.g.,



SCHEME 139

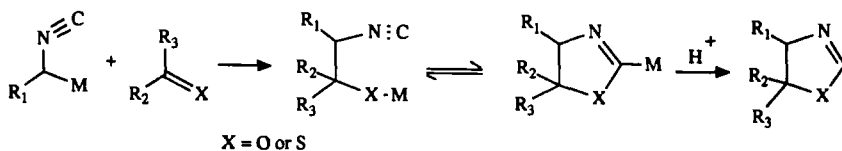
trimethyltin chloride) favoring the heterocyclic product [86TL5269; 87S693; 90H(31)1213], and hard electrophiles (e.g., trimethylsilyl chloride) the ring-opened form [87S693; 90H(31)1213]. A variety of different bases can be used, although lithium amides, such as LDA and especially lithium bis(trimethylsilyl)amide (LHMDS), have been reported to give superior results with oxazolines (91JOC6733).

With thiazolines it is still possible to obtain silylated heterocycles, despite the initial reaction giving the ring-opened product, since like the situation with oxazole (Section III,B,1) the desired isomerization can be induced thermally (Scheme 140) [90H(31)1213]. However, the analogous isomerization cannot be induced in the oxazoline case (87S693).



SCHEME 140

Oxazoline and thiazoline derivatives metalated at the 2-position can also be prepared by the combination of acyclic precursors, namely by the reaction of α -metalated isocyanides with ketones or thioketones (Scheme 141) [76LA183; 77AG(E)339; 79PAC1347]. Although this route is normally used to produce 2-unsubstituted derivatives via protonation, there is presumably no reason why other electrophiles could not also be utilized instead.

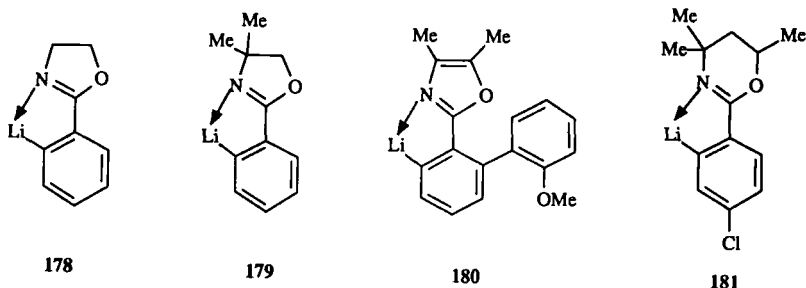


SCHEME 141

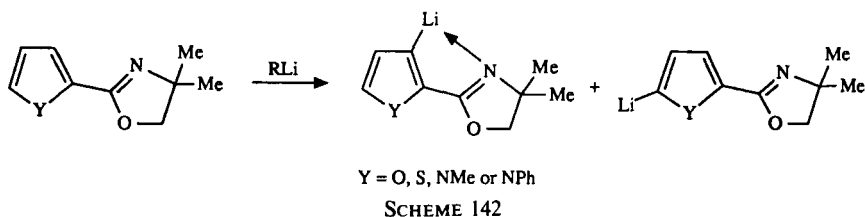
4. Oxazolines: Substituent Carbanions

A variety of heterocyclic systems containing unsaturated nitrogen can partake in directed aromatic or heteroaromatic lithiations. Pyrazole (II,D), tetrazole (II,G,2), imidazoline (V,B,2), and pyridine (IV,A,4) derivatives were discussed in the sections indicated. In addition, lithio derivatives of 2-oxazoline **178** (76LA183), 4,4-dimethyl-2-oxazoline **179** (79OR1; 85T837), 4,5-dimethyl-2-oxazole **180** (87CL19), and 4,4,6-trimethyl-2-oxazine **181** (79OR1) have all been successfully prepared.

The 4,4-dimethyl-2-oxazoline group has received a lot of attention because of its strong lithiation directing ability (76AG(E)270; 79OR1; 85T837), although competitive metalation experiments have shown that it is not as efficient a metalation director as alternative protected carboxyl derivatives such as dialkyl amides (79JOC4463, 79JOC4464; 80TL3355) or the 2-imidazoline group (91T9901). Despite this, however, it is still ca-



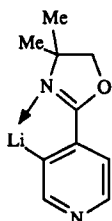
pable of directing metalation to the 3-position of thiophenes [77JOC-2649; 84T2107; 85JCS(P1)173], furans [82JCS(P1)1343; 92T149], and N-substituted pyrroles [82JCS(P1)1343, 82JOM(234)123], although as with pyridine, competitive 5-metalation also occurs (Scheme 142). Normally



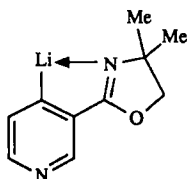
mixtures of both products are obtained, with the proportion of each being dependent upon the precise metalation conditions.

Exclusive metalation at the 3-position has been achieved in the furan case, after prior blocking of the 5-position with a trimethylsilyl group (90T2623), and 3,5-dilithiation has also been achieved with both the furan and thiophene derivatives (85TL5335). The dimethyloxazoline group has also been used in the direct metalation of pyridine (Section IV,A), and both the 3- and the 4-lithio derivatives **182** and **183** can be obtained under the appropriate conditions (82JOC2633; 85T837). However, because of the strong electron-withdrawing effect of the oxazoline group, care must be taken to avoid nucleophilic addition, at the pyridine 4-position, in the latter case [80JCS(P1)2070; 82JOC2633; 85T837; 86H125; 91JCS(P1)3165]. In addition to the above aromatic and heteroaromatic examples, the dimethyloxazoline group can also be used in alicyclic chemistry, as is shown by formation of the norbornene derivative **184** (91JOC5718).

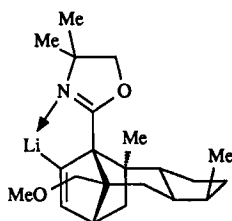
Directed *ortho*-metalation does not always occur with oxazoline compounds, as was shown by the chiral derivative **185** where competitive chelation of the *n*-butyllithium with the methoxy group prevented it from approaching close enough to abstract a proton from the benzene ring



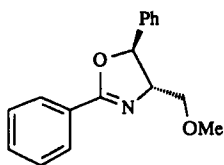
182



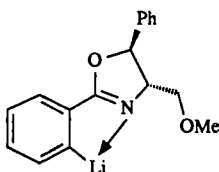
183



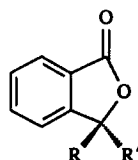
184



185



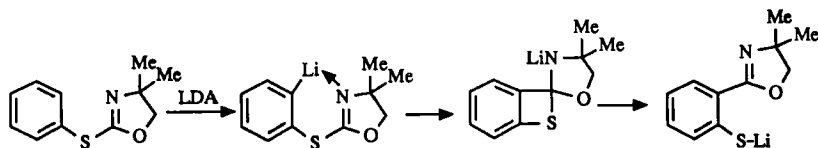
186



187

(83T1991). However, the desired lithio derivative **186** was successfully prepared via halogen-metal exchange on the analogous bromide, and subsequent manipulations led to the synthesis of chiral phthalides **187** (83T1991).

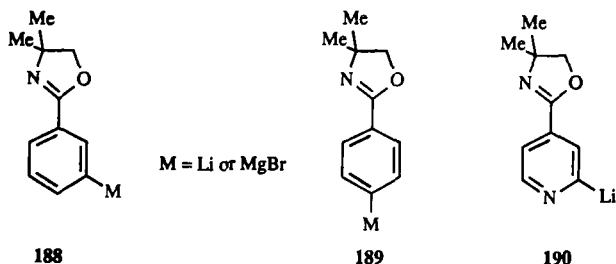
Examples of the direct lithiation of sites more remote from heterocyclic sp^2 -nitrogen are much less common, although evidence for direct δ -lithiation has been seen with 2-phenylthio-4,4-dimethyloxazoline, where migration of the oxazoline ring occurred as a result of nucleophilic attack by the initially formed δ -carbanion (Scheme 143) (83JOC2610).



SCHEME 143

Halogen-metal exchange represents a more facile route to remote carbanions, however, and both *meta* and *para* magnesium or lithium derivatives **188** and **189** have been obtained from the analogous bromides (70JOC6646; 74JOC2787; 90HCA417). The method can also be extended to the synthesis of heteroaromatic derivatives, as shown by the recent preparation of the 2-lithio-3-oxazolinyl pyridine derivative **190** (91MI3).

Halogen-metal exchange of benzene derivatives has also been used to

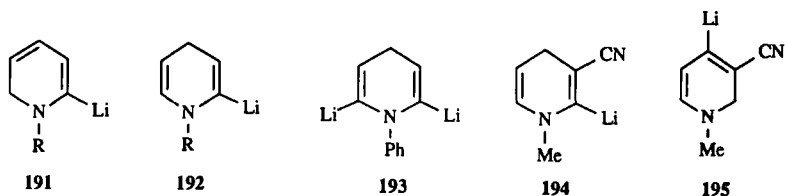


give *ortho*-metalation (70JOC6646; 74JOC2787), although in most cases it offers no advantage over direct lithiation.

C. PARTIALLY SATURATED SIX-MEMBERED RINGS

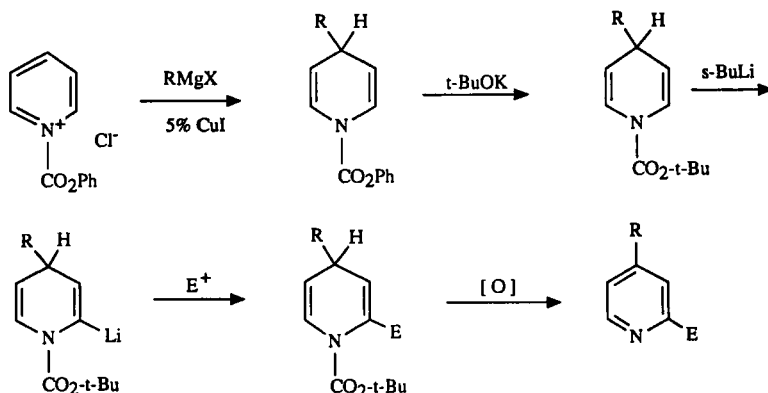
1. Dihydropyridines

1,2- and 1,4-dihydropyridines undergo direct metalation adjacent to the nitrogen atom and give the α -lithio derivatives **191** and **192**, respectively (79OR1; 82CRV223). The dilithio derivative **193** was obtained with 1-phenyl-1,4-dihydropyridine (75JOC563), and selectivity between alternative sites of metalation can also be achieved, as was shown by the formation of the 2-lithio-3-cyano derivative **194** with LDA (76CB2936). In fact, the directing effect of a nitrile group is strong enough to override the normal preference for α -metalation, as was shown by the formation of the γ -lithio derivative **195** from 3-cyano-1-methyl-1,2-dihydropyridine (76CB2936).

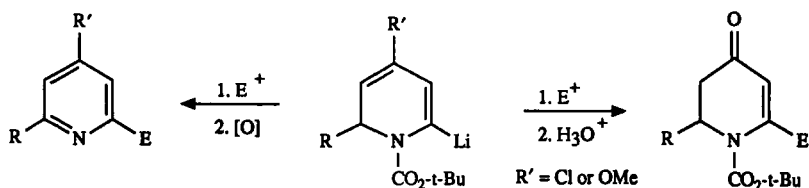


If the lithiated dihydropyridine contains a removable substituent on the nitrogen and if subsequent removal of the substituent is accompanied by oxidation then substituted pyridines can be obtained [88AHC(44)-199]. Thus, pyridine can be converted to a 1-(*tert*-butoxycarbonyl)-1,4-dihydropyridine by a two-step procedure involving initial copper-catalyzed Grignard addition to a 1-acylpyridinium salt, followed by

reaction with potassium *tert*-butoxide. Treatment with *sec*-BuLi gives the α -lithiated derivative, which can then undergo reaction with a variety of electrophiles (Scheme 144) (83TL2807).



When the 4-position is substituted, Grignard addition occurs at the 2-position, to eventually give a 2,4,6-trisubstituted pyridine via the 6-lithiated species (Scheme 145) (88TL1751). Alternatively, if the 4-substituent is a chloro (88TL1751) or methoxy group (89TL5053), the initial product can be hydrolyzed to an enone rather than being aromatized to a pyridine.

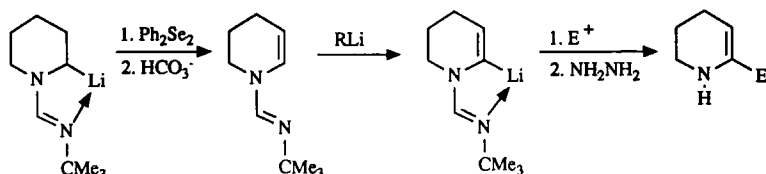


A variety of 3,4-disubstituted-1-(*tert*-butoxycarbonyl)-1,4-dihydropyridines have also been investigated, with lithiation being found to occur at either the C-2 or the C-6 positions. The relative proportions of the two products were dependent upon both the nature of the 3-substituent and the type of base employed (88JOC4437).

2. Tetrahydropyridines and Quinolines

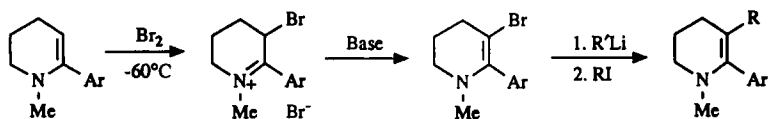
Metalation of 6-membered azaheterocycles is similar to that of their five-membered counterparts, and thus the *tert*-butylformamidine derivative of

1,2,3,4-tetrahydropyridine can be lithiated in a procedure (Scheme 146) that is entirely analogous to that seen with the related 2,3-pyrroline derivative (Section V,B,1) (85JOC1019).



SCHEME 146

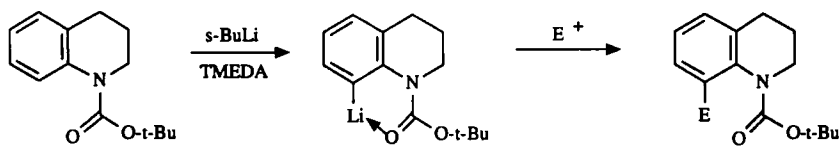
Direct β -metalation of a tetrahydropyridine has not been achieved, but as with exocyclic enamine systems (Section V,A,2), halogen-metal exchange has been performed successfully. Thus, 2-aryl-3-bromo-1-methyltetrahydropyridines have been metalated with either *n*-BuLi or *t*-BuLi, in a procedure that starts with bromination of the parent system to give an α -bromoiminium salt, which can then be deprotonated to give the desired β -bromo enamine (Scheme 147) [77JA8356; 82BSF(2)297]. If the



SCHEME 147

butyllithium is also used as the base, then the whole transformation can be performed in a "one-pot" procedure, with overall yields of 55–65% being obtained after alkylation with methyl or butyl iodide.

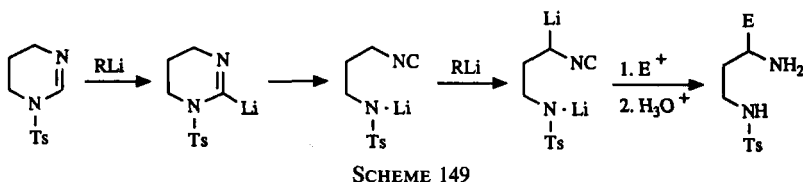
Because of lower steric constraints, *ortho*-metalation generally occurs more readily with six-membered ring-fused azaheterocycles than with five-membered species, and thus the directed β -metalation of 1,2,3,4-tetrahydroquinoline has been achieved in combination with a *t*-BOC protecting group (Scheme 148) (89TL1197).



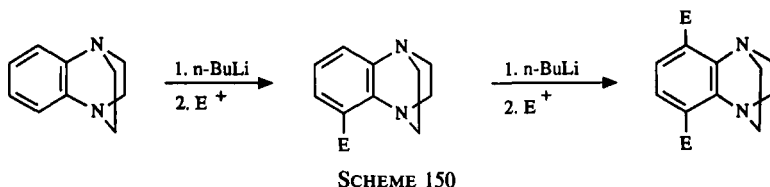
SCHEME 148

3. Reduced Diazine Derivatives

Very few results are available on the metalation of reduced diaza 6-membered ring systems, although 1-tosyl-1,4,5,6-tetrahydropyrimidine has been reported to give the 2-lithio derivative with *n*-BuLi or LDA (81LA103). However, the lithiation step is then followed by ring opening and further reaction with the base, to give a dianionic species that is then capable of undergoing electrophile addition at the metalated carbon atom (Scheme 149).



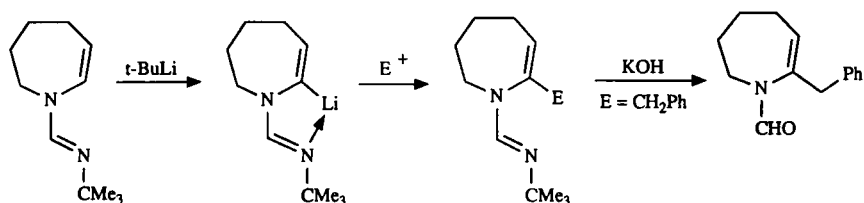
However, the directed β -metalation and derivatization of benzol[*b*]-1,4-diazabicyclo[2,2,2]octene has been successfully achieved, and in fact the whole process can be repeated next to the second nitrogen atom, provided that the initially added electrophile is stable to the metalation conditions (Scheme 150) (91KGS798).



D. SEVEN-MEMBERED AZAHETEROCYCLES

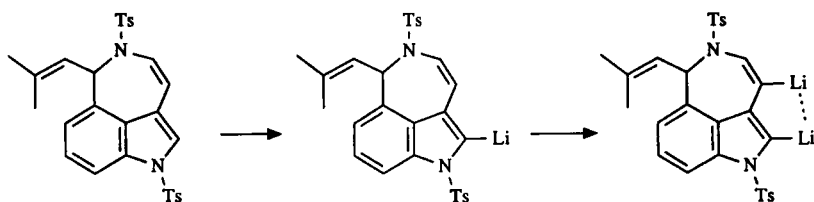
Seven-membered azaheterocycles such as azepines have received much less attention than their five- or six-membered counterparts, although, as with the related 2,3-pyrroline and 1,2,3,4-tetrahydropyridine compounds, the *tert*-butylformamidine derivative of azepine has been α -metalated with *t*-butyllithium (85JOC1019). In one case, instead of the normal deprotection involving hydrazine, hydrolysis of the formamidine protecting group was achieved with KOH to give the *N*-formylazepine derivative (Scheme 151) (85JOC1019).

β -Lithiation of a seven-membered azaheterocycle has also been observed with an azepino[5,4,3-*cd*]indole derivative (87JOC3319). Mono-



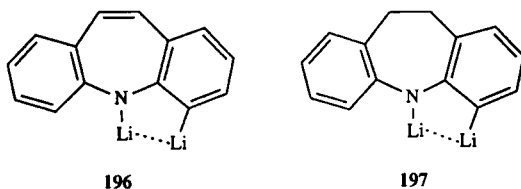
SCHEME 151

lithiation resulted in a normal α -lithiation of the indole ring, but dilithiation produced a β -lithiation with respect to the azepine nitrogen (Scheme 152), presumably as a result of an aggregation process involving the adjacent indole lithium atom.



SCHEME 152

Other seven-membered ring systems to have been successfully β -lithiated include 5*H*-dibenz[*b,f*]azepine and its 10,11-dihydro derivative (83JHC341; 84JHC197). The 4,5-dilithio derivatives **196** and **197** react successfully with electrophiles such as dialkylamides and D₂O to give 4-substituted derivatives. Mention of the lithiation of these systems has also occurred in the patent literature (71USP3624072).

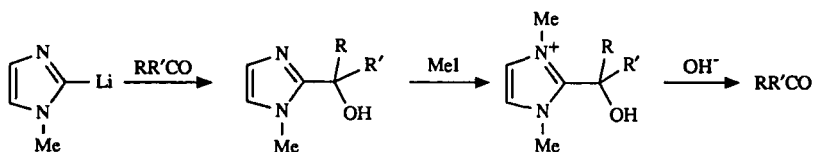
**196****197**

VI. Synthetic Utilization of Azaheterocyclic *sp*²-Carbanions

The synthetic utility of any carbanion depends first on its ability to be transformed to a stable derivative, and numerous examples of this type of reaction have been discussed in the previous sections. However, the initially produced compound may still be several steps away from the

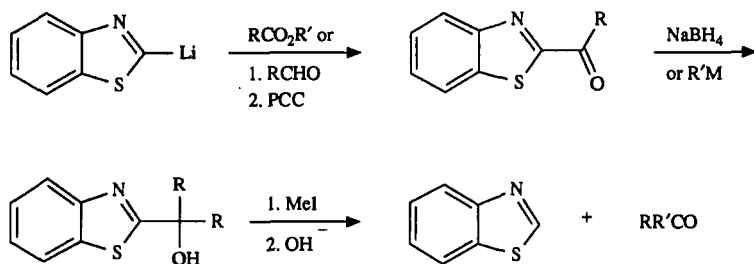
desired product, and in these cases the synthetic utility of the carbanion depends upon its ability to be converted to a species capable of undergoing further transformation. For example, five-membered heteroaromatic ring compounds can act as valuable intermediates in organic synthesis (86CRV795, 86CRV845), and often carbanion formation is an integral part of the overall sequence.

The utilization of benzothiazole as a carbonyl synthon, in a process that involves the intermediacy of the benzothiazole-2-anion, was discussed in Section III,C,4, but in addition, by a closely related process, the same species can also be used as a protecting group for the carbonyl function (85H2467; 91BCJ3256). This protective role is the same as that found earlier for 1-methylimidazole (Scheme 153) (84TL3251), with deprotection involving a quaternization step, which is then followed by basic hydrolysis.



SCHEME 153

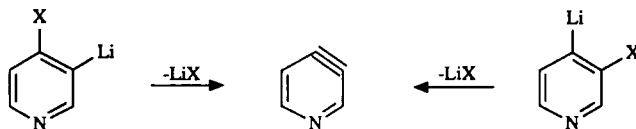
In the case of the benzothiazole system, both aldehydes and mixed ketones have been synthesized by reduction or alkylation of the appropriate carbonyl precursors. The carbonyl compounds are in turn prepared from the benzothiazole-2-anion either directly by reaction with esters or indirectly by reaction with aldehydes followed by PCC oxidation (Scheme 154) (85H2467; 91BCJ3256).



SCHEME 154

A common synthetic use of heterocyclic carbanions is as precursors of heterocyclic arynes (hetarynes), although the intermediacy of the latter species can often only be inferred from the structure of the isolated products [65AG(E)543, 65AHC(4)121; 67MI1; 71AG(E)20; 82T427]. However,

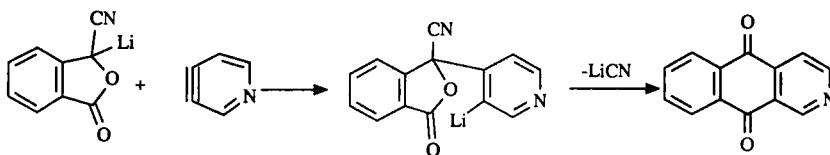
one azahetaryne whose synthesis and identity are well established is 3,4-didehydropyridine (3,4-pyridyne), which can be readily prepared by direct lithiation or halogen-metal exchange on the appropriately substituted halopyridine. Either 3- or 4-lithio derivatives can be used (Scheme 155),



SCHEME 155

since elimination of lithium halide gives rise to the same pyridyne, with the rate of halide loss being in the order $I > Br > Cl > F$ (80TL4137; 82T427).

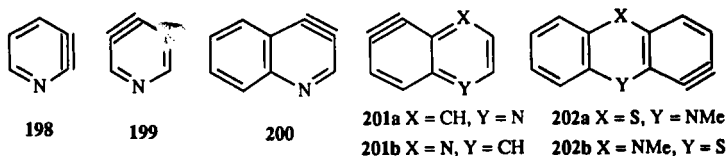
Substituted derivatives of 3,4-didehydropyridine have also been prepared, and these have been utilized in a variety of cycloaddition and nucleophilic addition reactions (82T427; 89ACR275). A recent example involves the synthesis of azaanthraquinones by reaction of the pyridyne with the lithium salt of 3-cyanophthalide (Scheme 156), in a sequence that also involves the intermediacy of a 3-pyridyl carbanion (88H2643).



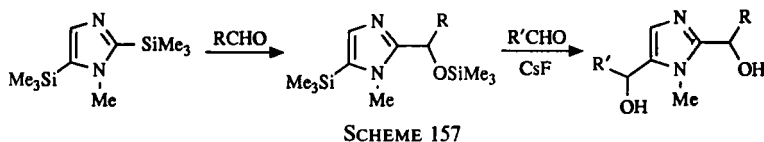
SCHEME 156

Formation of 2,3-didehydropyridine **198** by a carbanionic route is much less favorable than that for the 3,4-isomer, and normally this intermediate is prepared by alternative methods, although 3-pyridyl carbanions can still be used as a source where the presence of a blocking substituent in the 4-position prevents 3,4-pyridyne formation [69JCS(C)1973; 82T-427]. Other azahetarynes that can be synthesized via carbanion precursors include 4,5-didehydropyrimidine **199** and 3,4-didehydroquinoline **200**, as well as the carbocyclic 5,6- and 7,8-didehydroquinolines **201a** and **201b** (82T427). Similarly, derivatives of both 2,3- and 3,4-didehydro-10-methylphenothiazines **202a** and **202b** have recently been prepared [89H(29)485; 90H(31)2209].

Another class of carbanion derivatives that has received a lot of attention are the azaheterocyclic trialkylsilanes, which are readily obtained by reaction of the appropriate carbanion with trialkylsilyl halides. These compounds are capable of reacting directly as heteroaryl anion equivalents

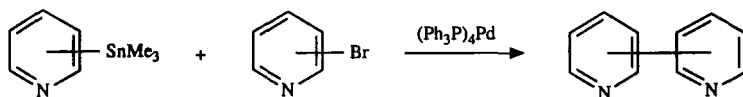


with many electrophiles. However, by the use of fluoride-induced carbon-silicon bond cleavage, they can also be used to generate a nonbasic carbanionic species that is further capable of undergoing *in situ* addition to a variety of electrophilic substrates. These include relatively acidic species such as enolizable aldehydes and ketones. Differing orders of reactivity, between different positions of substitution, mean that selective displacements can sometimes be achieved. Thus the 2-silyl substituent in 2,5-bis(trimethylsilyl)-1-methylimidazole can be replaced simply by heating with benzaldehyde, but similar reaction at the 5-position requires the use of fluoride catalysis (86MI2, 86MI3; 91CB1639). The synthetic utility of these processes is demonstrated by the fact that it is possible to use both types of reaction in sequence to give a variety of differently substituted 2,5-imidazole derivatives (Scheme 157).



Other examples of (trialkylsilyl)azaheterocyclic systems where direct reaction has resulted in ipso substitution of the silyl group include 2-pyridyl [69JHC433; 72JOM(38)29; 76JOM(104)153], 2-benzothiazolyl (71JHC257; 73CB594; 85TL5477), 1-methyl-2-imidazolyl and 1-methyl-2-benzimidazolyl (72JHC67), 1-methyl-2-pyrrolyl [72JOM(38)29], 2-thiazolyl (83TL2901; 88G211; 89JOC693; 90JOC1439), 5-thiazolyl (88G211), and 2-oxazolyl (88G211). Similarly, systems where fluoride-catalyzed reaction has been used include 2-benzothiazolyl (82TL5079), 5-thiazolyl (88G211), and 5-pyrazolyl (91CB1639).

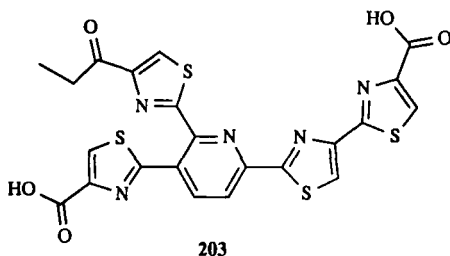
Trialkylstannyl groups can also be replaced by reactive electrophiles in certain cases, but most commonly stannylated azaheterocycles are employed in palladium catalyzed cross-coupling reactions [85PAC1771; 86AG(E)508; 92S413]. For example, trimethylstannylpyridines can be reacted with bromopyridines in the presence of catalytic amounts of tetrakis-(triphenylphosphine)palladium to give a variety of different bipyridines (Scheme 158)(86S564).



SCHEME 158

Other azaheterocyclic stannane derivatives to have been employed in palladium-catalyzed cross-coupling reactions with a variety of brominated or iodinated substrates include 3-quinolinyl (86S564), 1-methyl-2-pyrrolyl (86TL4407), 1-phenyl-3- and 4-pyrazolyl [92H(33)813], 2-thiazolyl (86TL4407; 87S185; 88G211), 4- and 5-thiazolyl (87S185; 88G211), 4-methyl-2-oxazolyl (87S693), 4,4-dimethyl-2-oxazolyl (87S693; 88-CL-1351), 5-isoxazolyl (89TL4249), 2-pyrimidinyl [90H(31)1155], 2-methyl-thio-5-pyrimidinyl [89JCS(P1)255], and the 5-substituted derivative of 1-benzyl-2(1*H*)-pyrimidinone [89JCS(P1)255]. Bis(trialkylstannyl) derivatives can also be used as a source of doubly substituted products, and successful azaheterocyclic examples include 2,5-dipyridyl (86S564) and 2,5-dithiazolyl (87S185).

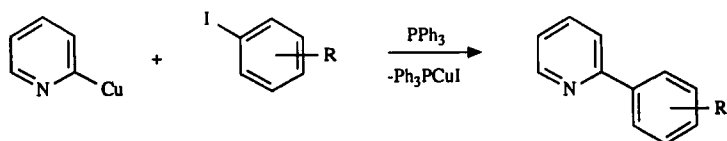
Mixed trialkylstannyl and silyl derivatives have also been used in coupling reactions, with subsequent replacement of the silyl substituent by bromine, leading to species that are capable of undergoing further coupling reactions. This process was amply demonstrated by the recent synthesis of micrococcinic acid **203**, which involved four palladium-catalyzed cross-coupling reactions on stannylated substrates, two palladium-catalyzed trimethylstannane replacements of bromine, two trimethylsilyl displacements by bromine, and a total of four bromine–lithium exchange reactions, on three different thiazole derivatives and one pyridine derivative (91-TL4263).



Palladium-catalyzed cross-coupling reactions are not restricted to stannane derivatives, however, and other azaheterocyclic carbanion derivatives to have been investigated include 1-methyl-2-pyrrolylmagnesium bromide and 1-methyl-2-pyrrolylzinc chloride (81TL5319), 1-methyl-2-indolylmagnesium bromide (81TL5319), 1-substituted-2- and 5-imidazolyl-

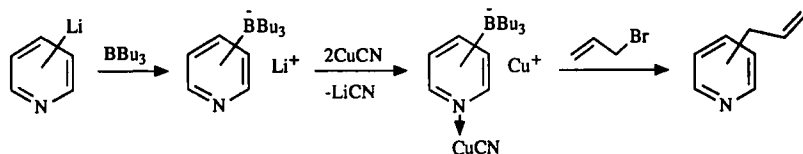
zinc chloride (88TL5013), and 2- and 3-pyridylzinc chloride (87S843). In addition, dialkylpyridylboranes, which are derived from the lithio carbanion by reaction with dialkylmethoxyboranes, have also been utilized in palladium-catalyzed reactions [84H(22)265, 84H(22)2475, 84S936; 85CPB-4755].

Other metals such as nickel have also been investigated for their ability to participate in catalyzed cross-coupling reactions (92S413), but normally with less success. Thus, only a 13% yield of 2,2'-bipyridine was obtained on attempted nickel-phosphine catalyzed coupling of 2-pyridylmagnesium chloride and 2-bromopyridine (82T3347). In contrast, 2-pyridylcopper, which was prepared by reaction of the lithio compound with CuI, underwent direct coupling with a variety of iodoarenes, when the reaction was conducted in the presence of one equivalent of triphenylphosphine (Scheme 159) (86T3981).



SCHEME 159

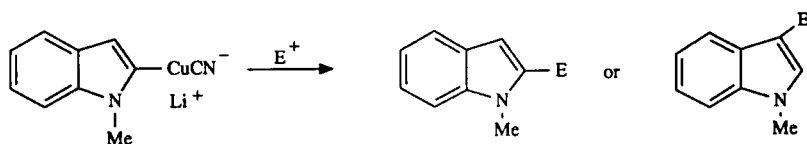
Another type of reaction involving copper occurs in the condensation of allylic bromides with copper(I) tributyl-3- and 4-pyridylborates, which are generated *in situ* by reaction of the lithium derivatives with CuCN (Scheme 160) (87JHC377). In this case two equivalents of CuCN are required because of coordination to the nitrogen atom.



SCHEME 160

Other azaheterocyclic borates to have been similarly utilized include the 3-quinoline, 4-isoquinoline, 1-methyl-2-pyrrole, and 1-methyl 2- and 3-indole derivatives (87JHC377).

Still another type of reaction involving copper occurs with (1-methyl-2-indolyl)cyanocuprate, which can give either 2- or 3-substituted products depending upon the nature of the electrophile, with the latter derivatives



SCHEME 161

being assumed to arise through initial π -complex formation (Scheme 161) (89CC727).

Finally, azaheterocyclic *sp*²-carbanions have often been used as vital intermediates in multistep syntheses of polycyclic heterocycles, including a variety of different natural products, and although discussion of these routes is beyond the scope of this article, the reader is directed to a number of other sources that cover different aspects of this, and related topics, in more detail. These include discussions on five-membered heteraromatic rings as intermediates in organic synthesis (86CRV795); synthesis of condensed heterocyclic compounds using heteroatom directed aromatic lithiation (87MI2); synthetic strategies for polysubstituted aromatics using directed *ortho*-metalation (90CRV879); synthetic approaches to the ellipticine alkaloids (90MI1; 90MI4; 91MI6); and metalation strategies for the functionalization of azines [91AHC(52)187].

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The Concept of Aromaticity in Heterocyclic Chemistry

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I. Introduction

Among the theoretical concepts that constitute the rational basis of modern organic chemistry, the concept of aromaticity is one of the most general but also controversial constructs. Designed as both an appropriate language for the analysis of specific features of structure, stability, and physical and chemical properties inherent in the conjugated cyclic molecular systems and for their quantitative or semiquantitative evaluation, the concept of aromaticity has received special attention in the chemistry of heterocyclic compounds. It was indeed recently emphasized that "it would be inconceivable to attempt to teach or practice heterocyclic chemistry without the use of the concept of aromaticity" (91H127). Therefore, each of the monographs (69MI1; 75MI1; 84MI1; 86MI1) and review papers (71TCC33; 80PAC1409; 85UK86) concerned with the concept of aromaticity have amply covered various aspects of its application to heterocycles. Several concise (72KGS1011; 85KGS867; 91H127) and one comprehensive (74AHC255) review papers devoted to the problem of heteroaromaticity also have been published. In the latter, the literature was covered up to the beginning of 1972, which justifies its updating along with an analysis of modifications employed and newly introduced indices and definitions of aromaticity. These are the main purposes that the present survey pursues.

It has been long recognized that despite all its versatility and usefulness, the very idea of aromaticity lacks a secure physical basis. No certain physical or physicochemical property whose measurement can be directly expressed in terms of aromaticity exists, but there are quite a large number of properties that are invoked to indicate aromaticity. The aromaticity

(antiaromaticity) of cyclic systems is, in the first place, manifested in the stabilization (destabilization) effects of cyclic electron (bond) delocalization and nonadditivity of the collective properties of a molecule. In the present review the viewpoint (74AHC225; 85UK86) is held that it is primarily energetic properties and, consequently, energetic criteria that ought to be used as the basis of an analysis of the concept of aromaticity.

Since empirical approaches to the evaluation of aromatic stabilization energies have been recently reviewed and didactically presented (91H127) the emphasis here is on more careful consideration of the current development of theoretical indices of aromaticity both previously employed and introduced in the last few years. Pertaining to the latter are topological resonance energy (TRE), resonance energy determined on the basis of the conjugated circuits model (CCMRE), aromatic stabilization (antiaromatic destabilization) energies estimated from the heats of isodesmic, homodesmotic, or hyperhomodesmotic reactions, the HOMO–LUMO energy gap, and the assessment of cyclic delocalization based on a study of topological characteristics of charge distribution in molecular systems. All of them proved to be useful tools in the analysis of physical properties and chemical behavior of heteroaromatic compounds.

The rapidly growing reliability of theoretical calculations of complex organic molecules and their reactions gradually leads to an establishment of a real partnership between experimental and theoretical branches of chemical science, the process that has been recently characterized as a "mutation of chemistry" (91JST5). This tendency is reflected in the present survey of heteroaromaticity by including the data of computational studies that are treated in parallel with experimental results and, with due regard for their accuracy, are considered as not only useful for the purposes of systematization and explanation but also as possessing appreciable predictive power. Inclusion of computational insight in a study of structure and reactivity of heteroaromatic and heteroantiaromatic compounds, some of the latter being elusive, allows one to analyze in more detail the dynamic structural aspects relevant to the problem. Understanding the close connection between structural rigidity or nonrigidity and aromaticity as well as the rearrangement and reaction modes governing a conversion of thermodynamically unstable antiaromatic species to aromatic ones has become the important constituent of the investigation of heteroaromatic and heteroantiaromatic compounds in the last decade.

In the first part of this review a critical analysis of various criteria of aromaticity and the indices quantifying aromatic or antiaromatic character is presented in Section II with an emphasis on application to heterocyclic compounds. Special attention is paid to the elucidation of general trends observed in the change of aromatic character on going from the parent

carbocycles to their various heterocyclic analogs (Section III). Particularly useful is the recently developed topological charge stabilization strategy. The applications of the concept of aromaticity to various classes of heterocycles are considered in Section IV following the approach featured in Section III. The material of these sections basically complements that of the previous survey in *Advances in Heterocyclic Chemistry* in 1974 (74AHC255). In the remainder (Sections V and VI), the extension of the concept of aromaticity and other relevant theoretical constructs to the rapidly progressing branches of heterocyclic chemistry on the border of organic and inorganic chemistry is considered.

This review should be regarded as neither the all-inclusive analysis of the present state of the problem of heteroaromaticity nor as an exhaustive compilation of literature sources. The literature has been covered up to the beginning of 1991.

II. Criteria of Aromaticity and Antiaromaticity

Although a good many criteria of aromaticity have been suggested (75MI1; 84MI1; 86MI1), there exists no yardstick according to which one might unambiguously assign a compound to the aromatic or antiaromatic type. The most important requirement that a criterion of aromaticity should meet is that it must be directly related to some known physicochemical property regarded as a manifestation of aromaticity and this one must be experimentally quantifiable. In some cases not all the chief criteria of aromaticity, namely, the energy, structural, and magnetic ones, are satisfied concurrently (87JA2902). This discordance may be accounted for by the fact that the criteria refer to different, mutually "orthogonal" groups (89JA7; 91H127). The analysis in the following section addresses the question what is a coherent system of interrelated, noncontradictory criteria of aromaticity?

A. ENERGETIC CRITERIA

The aromaticity (antiaromaticity) of a compound is associated for the experimentalist primarily with its stability (instability) against decomposition, valence isomerization, intra- and intermolecular cyclizations, recyclization reactions, etc. (75MI1; 84MI1; 86MI1). To characterize the reactivity of aromatic compounds a special term, regeneration, i.e., "the tendency to retain the type," has been introduced [72AG(E)404]. The original type of electronic system, lost at a certain reaction stage, is

restored in the products. Such regenerative (or meneidic) [72AG(E)404] behavior of aromatic compounds is regarded as a manifestation of the peculiar stability of their structural type. This was, apparently, a good reason for assigning the dominant role in determining aromaticity and, later, antiaromaticity to the energy criterion that rests on energy estimates of aromatic (antiaromatic) stabilization (destabilization). However, the stability (instability) of a compound characterized by cyclic electron (bond) delocalization may depend not only and even not so much on aromaticity (antiaromaticity) but rather on various other factors. Therefore, in order to classify a compound as aromatic, antiaromatic, or nonaromatic it is necessary to single out the effect of stabilization (destabilization) caused by the cyclic electron (bond) delocalization that used to be associated with the resonance energy (RE). In order to find the value of the RE a difference must be calculated between a quantity characterizing the experimentally found energy of a given molecule (such as heat of atomization ΔH_a or heat of formation ΔH_f) and the same characteristic obtained with the aid of some additive scheme. The essence of such a scheme is a deliberate choice of a proper model reference structure whose energy differs from that of the cyclic structure precisely by the component corresponding to the delocalization in question.

A solution of the problem of a reference structure meeting the above requirement was proposed by Dewar and deLlano (69JA789). They suggested the use of acyclic linear polyenes as the set of molecules for determining the values of bond energies, which then are employed to calculate the RE value of a given compound. Within the framework of this approach various schemes for the determination of the RE have been devised (69JA789; 70TCA235; 71JA305, 71JA2413, 71JCE509; 72T3657; 74JCE640; 76JA2750, 76JA6840; 77JA1692, 77MI1). The REs can be divided into two major classes, viz., the thermochemical type (TCRE) and the vertical one (79JA4832; 87JA363; 88JPC5036). The latter has to do with a variety of so-called quantum mechanical resonance energies (QMRE) (79JA4832; 87JA363). In the general case, the QMRE corresponds to the energy contribution made by electron delocalization as a whole but not by the part of it represented by the electron cyclic (bond) delocalization. For this reason, in calculating the general form of the QMRE the reference structure must possess isolated (noninteracting) double bonds (79JA4832) [In the VB scheme such a calculation takes into account the contribution from only one, the most stable, resonance structure (87JA363; 88JPC-5086).]

On the other hand, to apply Dewar's approach within the QMRE scheme, it would be necessary to normalize resonance energies, calculated in terms of the above model, with respect to butadiene in accordance with

the relationship (79JA4832)

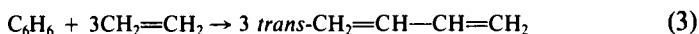
$$\text{QMRE (Dewar)} = \text{QMRE} - n\text{QMRE (butadiene)} \quad (1)$$

where n is the number of single bonds in the Kekule structure of the molecule.

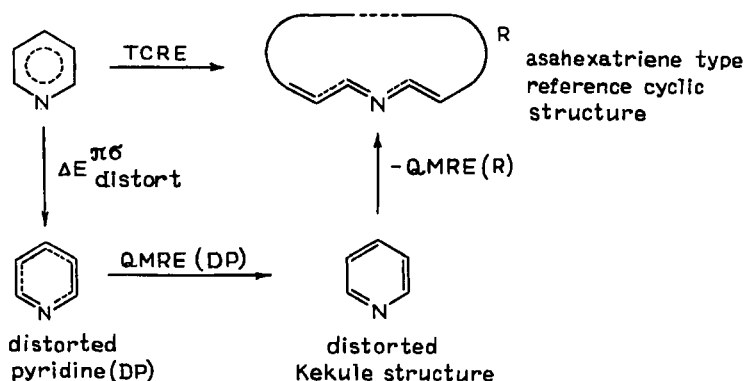
In calculating TCRE, the bond energies are determined from the energy of an acyclic polyene in its equilibrium geometry. The difference between TCRE and QMRE is shown in Scheme 1 in which $\Delta E_{\text{distort}}^{\pi\sigma}$ is the energy of distortion of the C_{2v} structure of pyridine into a C_s structure. We shall consider the most important schemes for calculating the RE such as those of Dewar, Hess-Schaad, and others. Particular attention will be given to estimates of RE based on isodesmic, homodesmotic, and hyperhomodesmotic reactions whereby the expressions for the values of bond energies found with a given set of molecules are substituted into the equation for the RE so that the problem is reduced to the determination of the RE from the enthalpy of the relevant reaction. For example, when calculating bond energies the experimental values of ΔH_a^0 are used for the set of the reference molecules CH_4 , CH_3CH_3 , $\text{CH}_2=\text{CH}_2$ and the calculation of the RE comes down to the evaluation of ΔH of the reaction



in which case $\Delta H = 64.2 \pm 1.7$ kcal/mol (84JCE225). With the molecules of CH_4 , $\text{CH}_2=\text{CH}_2$, *trans*-butadiene ($=\text{C}-\text{C}=\text{bond}$), the RE is determined in the form of the enthalpy of the reaction



where $\Delta H = 21.6 \pm 1.5$ kcal/mol (84JCE225).

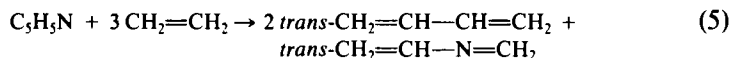


SCHEME 1

Consequently in the case of pyridine



where $\Delta H = 65.5 \pm 1.6$ kcal/mol (85TL5667) and



where $\Delta H = 25.4$ kcal/mol [calculated *ab initio* (85TL5667)].

Reactions (2) and (4) are isodesmic (70JA4896) (equal numbers of formal single and double bonds between the carbon atoms in reactants and products), and reactions (3) and (5) are classified as homodesmotic (75TCA121) [where, unlike (2) and (4), the number of bonds of every formal type is equal in reactants and products]. In both, particularly in reactions (3) and (5), the energy contribution to ΔH , stemming from the difference between the types of hybridization of carbon atoms as well as between the types of C(*sp*^{*n*})—H bonds in reactants and products, is reduced to a minimum.

Thus, the RE determined from the energy of an isodesmic reaction of bond separation is in fact QMRE-like and represents an estimate of various effects of electron delocalization. By contrast, the use of the homodesmotic reaction leads to a Dewar-type RE (75TCA121) allowing the evaluation of the contribution by precisely the cyclic electron (bond) delocalization.

1. Dewar Resonance Energy

Earlier definition of resonance energies comes down to an evaluation of the QMRE within the framework of the Hückel MO method (HMO) (61MI1; 75MI1; 86MI1). Hückel resonance energy (HRE) is defined as

$$\text{HRE} = \text{DE} = -(E_\pi - n_{\text{C}=\text{C}}(2\alpha + 2\beta)) \quad (6)$$

where *n* is the number of double bonds in the hypothetical Kekule-type structure and *E*_π is the π-electron energy of the conjugated molecule. Seeing that the HRE is used to evaluate the energy of the electron delocalization rather than the cyclic electron (bond) delocalization, the inadequacy of the HRE (DE) scheme in assessing the aromaticity or antiaromaticity is obvious.

By contrast, the Dewar resonance energy represents solely the contribution coming from the cyclic electron (bond) delocalization since the model reference structure is represented not by a system of isolated π-bonds, but by a hypothetical cyclic polyene with the number of π- and σ-bonds equal to that in a given molecule. Making use of the additivity of bond energies in acyclic polyenes (65JA692), one may calculate the total energy

of these by merely summing the energies of all π - and σ -bonds. The question of energy additivity in acyclic polyenes has been proved at different levels of approximation [69JA789; 78MI1; 83JA(103)7500; 85JA1161].

The Dewar resonance energy (DRE) is found as the difference between the heats of atomization of a given conjugated molecule and the classical Kekule reference structure

$$\text{DRE} = (\Delta H_a^m - \Delta H_a^{\text{add}}) \quad (7)$$

where ΔH_a^{add} is the heat of atomization calculated for the reference structure.

DRE values, some of which are given in Table I, have been calculated for a broad range of systems including heterocyclic compounds (69JA789, 69JA6321; 70TCA235; 71JCE509). These are well correlated with structural and magnetic criteria of aromaticity (see Sections II,B and II,C) as well as with data on the reactivity of given compounds in the Diels–Alder type of cycloaddition.

2. Hess and Schaad Resonance Energy

The DRE calculation scheme takes into account only two types of CC bonds, not accounting for the fact that the energy of an acyclic polyene depends on its branching. The π -energy of a branched acyclic polyene E_π (BP) is related to the energy of an isomeric linear polyene E_π (LP) by (75JCP3399)

$$E_\pi (\text{BP}) = E_\pi (\text{LP}) - 0.09 T \quad (\text{in } \beta \text{ units}) \quad (8)$$

where T is the number of branching sites in the polyene. Thus, a more detailed differentiation is needed between the values of bond energies that would correspond to the types of bonds.

Hess and Schaad classified the bonds in acyclic polyenes into eight types (71JA305; 74JCE640) depending on the number of attached hydrogens, and applied the DRE model for calculating Hess-Schaad resonance energies (HSRE) within the HMO method (71JA2413; 72JA3068, 72T3657; 75T295; 76JOC3508, 78JA5268; 80PAC1399).

In their classification, branching is implicitly taken into account. The expression for calculating the HSRE has the form (for the energy in β units)

$$\begin{aligned} \text{HSRE} = E_\pi (\text{conjugated molecule}) - & (n_{\text{H}_2\text{C}-\text{CH}} E_{\text{H}_2\text{C}-\text{CH}} \\ & + n_{\text{HC}=\text{CH}} E_{\text{HC}=\text{CH}} + n_{\text{H}_2\text{C}=\text{C}} E_{\text{H}_2\text{C}=\text{C}} \\ & + n_{\text{HC}=\text{C}} E_{\text{HC}=\text{C}} + n_{\text{C}=\text{C}} E_{\text{C}=\text{C}} + n_{\text{HC}=\text{CH}} E_{\text{HC}=\text{CH}} \\ & + n_{\text{HC}-\text{C}} E_{\text{HC}-\text{C}} + n_{\text{C}-\text{C}} E_{\text{C}-\text{C}}) \end{aligned} \quad (9)$$

The values of the HSRE have been calculated for a broad variety of heterocyclic compounds (Table I).

3. Topological Resonance Energy

The DRE and HSRE schemes have certain shortcomings. In attempting to extend them to radicals and ions [81JA(103)5052] difficulties arise in regard to their modification and introduction of new parameterizations; empirical parameters have to be used for reference bond energies (69JA789; 71JA305, 71JA2413; 74JCE640) whose number increases considerably in passing to heterocyclic systems (69JA6321; 70TCA235; 72T3657). These schemes cannot be applied in the case of excited states. The TRE scheme is free of those drawbacks.

The TRE scheme rests on the formalism of graph theory. For a conjugated hydrocarbon, the matrix of the Hückel Hamiltonian H and the adjacent matrix $A(G)$ of the corresponding molecular graph G [$A_{rs} = 1$ if the v_r and v_s vertices (atoms) are adjacent, otherwise it is zero] are related as (73MI2; 77MI1, 77MI2, 77MI3; 83MI1; 86MI2)

$$H = \alpha I = \beta A(G) \quad (10)$$

where I is the unit matrix, and α and β are the Coulomb and the resonance integrals, respectively. The characteristic polynomial $P(G;X)$ of the graph G is the characteristic polynomial of its adjacency matrix A

$$P(G;X) = \det |XI - A| \quad (11)$$

TABLE I
REPE, CALCULATED BY VARIOUS SCHEMES (69JA6321;
70TCA235; 74JCE640; 75T295; 77JA692;
78JA5268; 80JOC1738)

Compound	DRE (eV)	HSRE (β)	TRE (β)
Benzene	0.1448	0.065	0.046
Cyclobutadiene	-0.193	-0.268	-0.307
Pyridine	0.167	0.058	0.038
Pyrimidine	0.146	0.049	0.032
Pyrazine	0.124	0.049	0.022
Azete	-0.168	-0.160	-0.1936
1,3-Diazete	—	-0.113	-0.1356
Pyrrole	0.038	0.039	0.040
Furan	0.031	0.007	0.007
Thiophene	0.047	0.032	0.033
Quinoline	0.148	0.052	0.036
Isoquinoline	0.148	0.051	0.033

The characteristic polynomial of a conjugated system may be constructed on the basis of Sachs theorem (77MI4; 83MI1; 86MI2) according to which the coefficients a_n of the characteristic polynomial $P(G; X)$ are given by the relationship

$$a_n = \sum_{s \in S_n} (-1)^{c(s)} 2^{r(s)} \quad a \leq n \leq N \quad (12)$$

where N is the number of vertices of the graph S , and $c(s)$ and $r(s)$ denote the total number of, respectively, components and cycles in the Sachs graph, S ; S_n is the set of all Sachs graphs with n vertices. In Eq. (12) the summation is performed over all Sachs graphs; a_n is the coefficient of $P(G; X)$ with $a_0 = 1$. Thus, the polynomial $P(G; X)$ may be written as

$$P(G; X) = \sum_{n=0}^N \sum_{s \in S_n} (-1)^{c(s)} 2^{r(s)} X^{N-n} \quad (13)$$

Then the total π -electron energy

$$E_\pi(\text{conjugated molecule}) = \sum_{i=1}^N g_i X_i \quad (14)$$

where X_i ($i=1, 2, \dots, N$) are the roots of the characteristic polynomial $P(G; X)$ and g_i is the occupational number of the i th MO.

For calculating the TRE by means of Eq. (15) E_π of the reference structure must be defined. This differs from E_π of the conjugated molecule in the absence of a contribution coming from cyclic electron (bond) delocalization. Or, in terms of graph theory, a polynomial must be constructed for the reference structure with only the acyclic Sachs graphs for the given molecular graph taken into account (76MI1; 77JA1692; 77MI4):

$$\text{TRE} = E_\pi(\text{conjugated molecule}) - E_\pi(\text{reference structure}) \quad (15)$$

The relevant polynomial corresponding to the reference structure is called the acyclic (77JA1692, 77MI4) or reference (76JA2750, 76JA6840) polynomial and since $r(s) = 0$, it has the form

$$R(G; X) = \sum_{n=0}^N \sum_{s \in S_n} (-1)^{c(s)} X^{N-n} \quad (16)$$

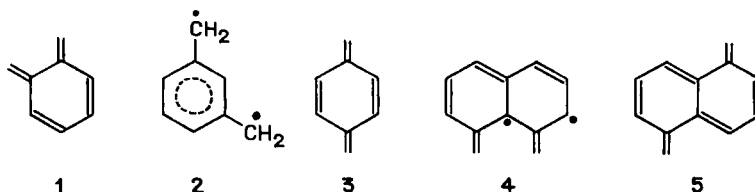
$$E_\pi(\text{reference structure}) = \sum_{i=1}^N g_i^{ac} X_i^{ac} \quad (17)$$

Thus, the formula for the TRE has the form (76MI1; 77JA1692, 77MI1)

$$\text{TRE} = \sum_{i=1}^N (g_i X_i - g_i^{ac} X_i^{ac}) \quad (18)$$

This expression shows that for acyclic polyenes $\text{TRE} = 0$.

The straightforward and elegant determination of the energy contribution coming from the cyclic electron (bond) delocalization makes the TRE scheme very attractive even though ambiguities still exist in its consistent application [79CPL595; 80TCA89; 81CPL(77)567; 82CPL(85)377]. For example, the TRE values may be manifestly overestimated in calculations on nonclassical structures. Thus, of three isomeric quinodimethanes (1–3) the *meta*-isomer has the maximum value of the TRE even though it is a highly reactive biradical (80TCA89). An extremely reactive, unstable, and, in some cases, merely hypothetical polyradical species (4) turns out to be more aromatic ($\text{TRE} = 0.209$) than its relatively stable singlet ground-state isomer (5) ($\text{TRE} = 0.151$) [81CPL(77)567].



A satisfactory assessment of aromaticity or antiaromaticity can also be made when the TRE scheme is extended to cover heterocyclic molecules (76MI1; 77MI1). The per electron values of the DRE, HSRE, and TRE given in Table I show in most cases the same trend. [Since the total resonance energies of molecules of different sizes cannot be compared, the following specific resonance energies are used to this end: per electron (REPE) (74JCE640; 77MI1; 80JOC1738); per bond (REPB) (77BCJ3057); per atom (REPA) (80PAC1471); per hundred (%RE), which is the ratio between the RE and the reference energy multiplied by 100 (79BCJ2202); and per face for the polyhedral structures (78JA3339).] A number of correlations have been established between the values of TRE and HSRE (78MI1) as well as TREs and magnetic susceptibilities [80BCJ1163; 81JA(103)5704; 88JMS(181)245]. The generality of the TRE scheme is well stressed by its applicability to radicals and ions (76MI1; 80JOC1738), excited states (78BCJ1788; 85JA4419), and organometallic compounds (85BCJ3617) as well as σ -aromatic (σ -antiaromatic) systems [88-JST(181)93] and three-dimensional molecules, such as C_{12} (90MI1), C_{60} -footballene (88BCJ2657), and bridged polyenes (87MI1). This scheme allows also the calculation of the TRE for Möbius systems [78BCJ1788, 78MI2, 78ZN(A)214; 86MI3; 87MI1].

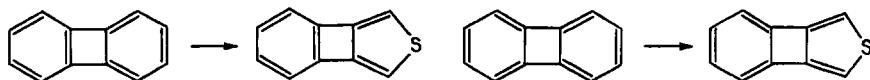
4. The Conjugated Circuits Model

There also are basically different approaches to studying the aromaticity (antiaromaticity) of polycyclic molecules that permit the determination of resonance energies without having recourse to quantum chemical calculations. One of these is represented by the conjugated circuits model, which was found to be particularly valuable in the case of large polycyclic systems (77JA444, 77T1905; 80IJQ549; 83PAC347; 85JA849; 86MI4; 88CCC2023; 89JST(183)29, 89JST(185)249, 89JST(188)223, 89MI1, 89PAC2107). A conjugated circuit is defined as a circuit within an individual Kekule valence structure in which there is a regular alternation of the formal CC single and double bonds (77JA444). Such circuits necessarily are of even length and either of a $(4n+2)$ or $(4n)$ type. The former are denoted by R_n , the latter by Q_n . The total number of sets of disjointed conjugated circuits within a single Kekule structure is $k-1$, where k is the number of Kekule valence structures for a given conjugated (hydrocarbon or heterocyclic) system [77JA444; 89JMS(188)223].

Different circuit counts are designated as $\#^{(4n+2)}$ or $\#^{(4n)}$ and are obtained by the summation of all $(4n+2)$ or $(4n)$ conjugated circuits. When the conjugated circuits model (CCM) is applied, the RE of a polycyclic conjugated molecule (CCMRE) may be determined as follows, taking into account that the REs are additive within the model in question (76CPL68),

$$\text{CCMRE} = \frac{1}{k} \sum_n (R_n \#^{(4n+2)} + Q_n \#^{(4n)}) \quad (19)$$

where R_n and Q_n are the parametric values for the conjugated circuits of $(4n+2)$ and $(4n)$ type, respectively, containing carbon atoms only. For $n > 3$, the terms R_n and Q_n are neglected since their energy contributions rapidly diminish with growing circuit size (increase in n). The numerical values of R_n ($n=1$ to 3) are obtained by means of a parameterization procedure with respect to the DRE values calculated for benzene, naphthalene, and anthracene [76CPL68; 89JMS(183)29]. The CCMRE method has in recent years been extended to cover various types of radicals, ions, excited states of hydrocarbons, and heterocyclic conjugated molecules [85JA849; 88CCC2023, 88JMS(181)111] as well. For the CCMRE calculations on heterocyclic molecules, such as the ones containing divalent sulfur, a Kekule-type structure is generated from the structure of polycyclic conjugated hydrocarbon by replacing the $-\text{CH}=\text{CH}$ fragment with $-\text{S}-$. This is exemplified by the case of 2-thianorbiphenylene [88JST(181)111].



5. *Estimation of Energies of Aromatic Stabilization and Antiaromatic Destabilization from the Energies of Isodesmic, Homodesmotic, and Hyperhomodesmotic Reactions*

As has been noted in Section II,A,1, depending on the choice of compounds from which the bond energies are to be determined, one may utilize either the scheme of the isodesmic reaction (2), (4) or that of the homodesmotic reaction (3), (5). The former belongs to the class of so-called bond separation reactions (70JA4896) in which all formal bonds between nonhydrogen atoms in a given molecule are separated due to the formation of the simplest (two-heavy-atom) molecules containing bonds of the same types. In an isodesmic reaction the number of bonds of each formal type is retained, even though the environment in which these bonds are located has been altered. For any molecule that may be represented with the aid of a classical valence structure a unique isodesmic bond-separation reaction may be thought of. Some energies of such reactions are given in Table II. The stabilization energy serves as the estimate of the total energy of conjugation rather than of only the cyclic (bond) delocalization energy. In other words, the thus determined RE corresponds to the HRE. Other components, for example, the strain energy, may also play a significant role. In order to separate these contributions, a combination of two isodesmic reactions may be used.

A better agreement between the bond types in conjugated cyclic and reference systems may be achieved by use of the scheme of homodesmotic reactions (75TCA121). In these reactions, which are a subgroup of isodesmic ones, reactants and products contain equal numbers of the carbon atoms in the corresponding states of hybridization; moreover, there is the matching of the carbon-hydrogen bonds in terms of the number of hydrogen atoms joined to the individual carbon atoms.

The energy of the homodesmotic reaction does not exclusively reflect the effect of cyclic (bond) delocalization. The reference structure is hypothetical and one cannot write the equation of a reaction, where a cyclic and an acyclic structure participate, for which the difference between the energies of products and reactants was determined by a single factor, namely, aromatic stabilization (antiaromatic destabilization) (75TCA121).

The homodesmotic reaction scheme has gained wide acceptance for evaluating the aromatic stabilization (antiaromatic destabilization) of carbocyclic and heterocyclic molecules [76JCS(P2)1222; 77JCS(P2)1036; 82PAC1129; 84JPC1467; 85JA289, 85TL5667; 86PAC129; 88JA4204]. In calculating their homodesmotic stabilization energies (HSE) similar results are obtained when experimental values of ΔH_f are used (75TCA121; 84JCE225; 85TL5667), or ΔE values are calculated by semiempirical [76JCS(P2)1222] and *ab initio* [76JCS(P2)1222; 77JCS(P2)1036;

TABLE II
STABILIZATION ENERGIES (IN kcal/mol) FOR ANNULENES AND THEIR HETEROANALOGS,
CALCULATED BY MEANS OF THE SCHEMES OF ISODESMIC (ISE), HOMODESMOTIC (HSE),
AND HYPERHOMODESMOTIC (HHSE) REACTIONS [82PAC1129; 83JA(103)7500; 85TL5667;
86PAC129; 88JA4204]

Compound	ISE		HSE		HHSE
	Exper.	Calc.	Exper.	Calc.	
Benzene	64.1	58.1 (6-31G*)	21.6	27.1 (MP4/6-31G*)	23.4 (6-31G*)
Cyclobutadiene	—	—59.5 (6-31G*)	—	—79.7 (MP4/6-31G*)	—84.6 (6-31G*)
Pyridine	65.5	60.7 ^a (6-31G*)	—	25.4 (6-31G*)	—
Pyrimidine	80.4	69.2 (3-21G)	—	—	—
Pyrazine	—	63.8 (3-21G)	—	—	—
1,3-Diazete	—	—64.5 (4-31G)	—	—95.0 (4-31G)	—
Silabenzene	—	46.84 (3-21G*)	—	—	16.02 ^b (3-21G*)
Pyrrole	—	43.80 (3-21G*)	—	—	5.62 (3-21G*)
Furan	—	35.19 (3-21G*)	—	—	5.0 (3-21G*)
Thiophene	—	32.54 (3-21G*)	—	—	9.80 (3-21G*)

^a 71.1 (3-21G).

^b Corrected for scaled ZPVE, uncorrected HHSE = 17.97.

82PAC1129; 84JPC1467; 85JA289; 88JA4204] methods. This finding opened up the possibility of determining by *ab initio* calculations also the heats of formation of subject molecules (85JA1904, 85JA5059; 89JA5675). Hence the accuracy of such calculations of ΔE for homodesmotic reactions has been thoroughly tested and compared with available experimental data [77JCS(P2)1036; 85JA5059; 88CPL(152)402; 89JA5675].

The HSE values estimate the contribution by cyclic (bond) delocalization, whereas the ΔE values for the isodesmic reaction (ISE) [76JCS(P2)1222] refer to the stabilization energy associated with conjugation as a whole; clearly, the latter values turn out appreciably larger, cf. HSE (4), (6) and ISE (3), (5).

An analog of the HSRE value, the hyperhomodesmotic stabilization energy (HHSE) takes account of the distinctions between various kinds of bonds in a more subtle way than the HSE scheme does.

Estimation of the aromaticity (antiaromaticity) of various compounds from the values of the ISE, HSE, and HHSE will be discussed in their respective sections. For the present, we will merely observe that these values, some of which are given in Table II, correlate with those of the HSRE and TRE.

The HSE (HHSE) scheme has been used increasingly in recent years; it has become, apparently, the most dependable tool for obtaining numerical values of the RE. This is partly explained by the growing amount of experimental thermodynamic data on organic compounds, but a still more important reason lies in the rapid development of the *ab initio* methods that enable the HSE values to be calculated even when some experimental data are absent. The TRE and CCMRE schemes have, however, a strong side: the possibility that they may provide the derivation of analytical expressions that could predict trends in the variation of the RE.

B. STRUCTURAL CRITERIA

The formulation of structural criteria rests essentially on the idea that the π -delocalization is the factor that causes the aromatic stabilization. The following manifestations of π -delocalization are considered in the connection: the planar geometry of the ring as a factor dictated by the requirement for better overlap of the p_π -orbitals, equalization of the lengths of the bonds in the ring, and the correspondence of the most symmetrical structure to a minimum on the potential energy surface (PES).

Structural indices constructed in this fashion are, in essence, phenomenological, and one is entitled to ask whether the specific features in the geometry of the aromatic and antiaromatic molecules are indeed determined, and if so, to what degree, by the cyclic electron (bond) delocalization.

1. *Distinguishing Characteristics in the Geometry of Aromatic and Antiaromatic Molecules*

Aromatic, antiaromatic, and acyclic polyenes primarily differ in bond lengths, which serves as a basis for the structural indices of aromaticity reflecting the degree of alternation of bond lengths in a ring.

Whereas the benzene molecule possesses a structure of D_{6h} symmetry with equal lengths of the CC bonds, for acyclic polyenes alternation of bond lengths is a characteristic [87JCS(P2)S1]. For antiaromatic molecules, alternation is even more pronounced and unlike the aromatic molecules, a high-symmetry structure of the lowest singlet state of the antiaromatic molecules does not correspond to a minimum on the PES. For

However, in recent years this basis has been somewhat undermined due to a critical reappraisal of experimental data on the benzene structure which, surprisingly, showed that a rigorous experimental proof of the generally accepted D_{6h} structure of benzene is actually nonexistent! It turned out that the X-ray structural data for benzene are compatible not only with the crystallographically ordered D_{6h} structure but also with the disordered D_{3h} model associated with superposition of Kekule-type benzene molecules rotated by 60° with respect to each other about the threefold axis, both static and dynamic types of disorder being conceivable [87AG(E)782]. It has been shown by very simple calculations that if the difference between the C—C and C=C bond lengths in the D_{3h} form is 0.10 \AA (which means the superimposed carbon atoms are only 0.058 \AA apart), the disorder contribution is as small as 0.0008 \AA^2 , which does not allow one to discard a possible D_{3h} -disordered model on experimental grounds even at very low temperature.

Other studies, such as infrared and Raman spectra of gaseous benzene, neutron diffraction studies of crystalline benzene, and electron diffraction and microwave spectral studies, are equally incapable, according to critical analysis [87AG(E)782], of resolving unanimously the D_{3h} — D_{6h} structural dilemma of the benzene molecule. Furthermore, no decisive conclusion could be drawn from photoelectron spectra or ^1H —NMR spectrum measurements of benzene molecules in a liquid crystal environment. The latter experiments merely indicate that the average lifetime of a D_{3h} structure (if it appears on the PES) is less than 10^{-4} sec corresponding to the energy barrier of the $D_{3h} \rightarrow D_{6h} \rightarrow D_{3h}$ interconversion of approximately 12 kcal/mol.

Therefore, quite paradoxically, we are faced with the fact that contrary to commonly accepted opinion, alternative D_{6h} and D_{3h} models of the benzene molecule cannot be distinguished on experimental grounds, and the former structural model had been assumed to interpret experimental data.

Bearing all this in mind, a special role in resolving the D_{3h}/D_{6h} problem ought to be assigned to its reliable quantum mechanical treatment, which unequivocally point to the fully symmetric D_{6h} structure [85JA5059; 87AG(E)782, 87AG(E)1298, 87JA363]. According to results of *ab initio* calculations the D_{3h} structure (9) of benzene possesses a higher energy than the D_{6h} structure (8). It is noteworthy that the D_{3h} structure does not correspond to a stationary point on the potential energy surface.

Another important conclusion stemming from theoretical analysis is that addressing the question of the origin of the trend to equalization of the CC bonds in the benzene ring. It has been shown, based on the semiquantitative second-order Jahn–Teller effect, that a 6π -electron configuration of the benzene molecule possesses its lowest energy in the geometry conforming not to a fully symmetrical D_{6h} but rather to a D_{3h} structure with the CC bonds of alternating lengths (66MII).

Thus, the archetype aromatic molecule of benzene owes its high-symmetry structure to the σ -skeleton. In the last few years this conclusion has been substantiated and its consequences extended to heterocyclic systems based on the curve-crossing diagram model (85JA3089, 85JOC4659; 86JOC3908; 87JA363; 88IC2219). *Ab initio* calculations at different levels of approximation have been carried out in order to estimate quantitatively π - and σ -components of the energy required to distort some fully symmetric carbo- and heterocyclic D_{6h} and D_{4h} structures to corresponding D_{3h} and D_{2h} forms with alternating bonds in the rings. The results are listed in Table III.

The D_{6h} hexagonal structure of benzene is indeed related to the value of $\Delta E_{\text{dis}}^{\sigma}$ exceeding that of $|\Delta E_{\text{dis}}^{\pi}|$. The lower σ -resistance of hexazine

TABLE III
DISTORTION ENERGIES ΔE_{dis} AND QMREs (IN kcal/mol) FOR BENZENE, CYCLOBUTADIENE,
AND THEIR HETEROANALOGS ACCORDING TO CALCULATIONS
(76JA2750; 87JA363; 88IC2219)^a

Molecule	$\Delta E_{\text{dis}}^{\pi, \sigma}$	QMRE	$\Delta E_{\text{dis}}^{\sigma}$	$\Delta E_{\text{dis}}^{\pi}$	$\Delta E_{\text{dis}}^{\pi}/\text{PB}^b$
Benzene, (CH) ₆	7.2	85	16.3	-9.1	-3.03
Cyclobutadiene (singlet), (CH) ₄	-3.4	30	7.6	-11.0	-5.50
Hexazine, N ₆	0.4	103	13.7	-13.4	-3.35
Tetrazet, N ₄	-5.5	108	9.2	-14.7	-7.35
Hexasilabenzene, (SiH) ₆	3.2	42	5.3	-2.1	-0.07
Tetrasilacyclobutadiene, (SiH) ₄	0.6	18	2.7	-2.1	-1.05
Phosphabenzene	1.0	44.1	3.8	-2.8	-0.93

^a Distortion energies ΔE_{dis} were calculated with 6-31G basis set and inclusion of π -space CI; the same basis set was used for QMRE calculations.

^b Per a π -bond.

N₆ and, at the same time, higher π -distortion involves a lesser stability of the D_{6h} structure, which is in agreement with *ab initio* calculations reported in Saxe and Schaefer [83JA(105)1760].

In calculating ΔE_{dis} for the D_{3h} benzene structure a geometry was assumed that would arise as a result of a distortion of the D_{6h} symmetry structure, with nuclear repulsion between carbons remaining constant [$R(\text{C}=\text{C}) = 1.34 \text{ \AA}$ and $R(\text{C}-\text{C}) = 1.4627 \text{ \AA}$] (85JOC4659; 87JA363). Although this approach was criticized, particularly on the grounds that a more rational choice would be that of the average length for internal C=C bonds in conjugated linear polyenes. The results of Hyberty *et al.* (85JOC4659; 86JOC3908; 87JA363) were later borne out by *ab initio* calculations (88JOC4889) with geometry optimization where the preset values were only those of the HCC angles imitating the effect of the Mills-Nixon type of deformation of the benzene ring.

Hyberty *et al.* (85JA3089; 86JOC3908; 87JA363) have arrived at the following important conclusion: "the connection between aromaticity-antiaromaticity and geometry is not meaningful in a broad sense" (88JPC5036) (having in mind that aromaticity or antiaromaticity is reflected in the values of the QMRE rather than in π -distortions).

This conclusion, nevertheless, should not be considered categorical but it points to the necessity of careful consideration of the correlation between the $\Delta E_{\text{dis}}^{\pi}$ value and the part of it that relates to cyclic electron delocalization. It has been shown by use of TRE calculations of aromatic benzene and antiaromatic cyclobutadiene molecules that in the case of benzene the distortion into a Kekule-type structure is characterized by a change of the aromatic cyclic π -electron delocalization energy in an opposite direction

to the total π -electron energy $E_\pi(\beta)$, whereas in the case of the antiaromatic cyclobutadiene these values change in the same direction. This behavior pattern bears witness to the validity of the structural criteria verified for a good deal of quite diverse structures of aromatic molecules. Next we briefly examine the main types of these criteria.

2. Indices of Aromaticity Based on Estimates of Bond Length Alternation in a Ring

The ideas of equality of carbon-carbon bond lengths as a characteristic attribute of a stable aromatic molecule (61JCS859; 64PAC363) were embodied in the form of the aromatic stability index of Julg (76TCA249).

$$A = 1 - \frac{225}{n} \sum_r^n \left(\frac{d_r - \bar{d}}{\bar{d}} \right)^2 \quad (21)$$

where d_r is the length of the r th bond and \bar{d} is the average length of n peripheral bonds (in Å). Later this expression was modified to take into account the requirement for uniform distribution of the electron density along the molecular ring bonds (71MI1)

$$A = \left[1 - \frac{225}{n} \sum_r^n \left(\frac{d_r - \bar{d}}{\bar{d}} \right)^2 \right] \frac{n}{[r]} \left(\frac{\Delta q_r}{d_r} \right)^2 \quad (22)$$

where $\Delta q_r/d_r = (q_\mu - q_\nu)/d_r$ is the charge gradient over the r th CC bond between the atoms μ and ν . Expression (22) proved useful for estimating the aromaticity of heterocyclic molecules [81JOM(215)315].

The shortcoming of this index is that it takes into account only peripheral CC bonds and thus is incapable of a subtler differentiation of the aromaticity of polycyclic molecules (85KGS867). It also cannot be applied in the case of such conjugated heterocyclic compounds as, e.g., 1,3,5-triazine. In Eqs. (21) and (22), the mean value of the CC bond was taken as the reference bond length, but it should be kept in mind that, for example, for polyacenes the value of \bar{d} grows with an increase in molecular size (68CJC2027). These drawbacks were partly circumvented in the aromaticity index [harmonic oscillator model of aromatic stability (HOMAS) (72TL3839)] as well as in the ΔN (85KGS867) and V [68CJC2027; 72TL3839; 81JOM(215)315; 85T1409; 86T89; 87T4725] indices based on estimates of the variation of bond orders of the heterocycles. In the HOMAS model, in place of \bar{d} the optimal value of the bond length d_{opt} is used as determined from experimental data on CC bond lengths in ethane (s , "pure" single bond) and in ethylene (d , "pure" double bond) and on k ,

the force constant ratio for stretching modes of "pure" single and double bonds (23) (75CJC945). The value of d_{opt} (CC) equals 1.397 Å for other bonds it is 1.338 (CN), 1.308 (NN), and 1.300 (CO) Å (75CJC945)

$$d_{\text{opt}} = \frac{s + kd}{1 + k} \quad (23)$$

$$\text{HOMAS} = 1 - \frac{98.89}{n} \left\{ \sum_{r=1}^{n_{\text{CC}}} (d_{\text{opt}}^{\text{CC}} - d_r)^2 + \sum_{r=1}^{n_{\text{CX}}} (d_{\text{opt}}^{\text{CX}} - d_r)^2 + \sum_{r=1}^{n_{\text{CY}}} (d_{\text{opt}}^{\text{CY}} - d_r)^2 + \sum_{r=1}^{n_{\text{XY}}} (d_{\text{opt}}^{\text{XY}} - d_r)^2 \right\} \quad (24)$$

where n_{CC} , n_{CX} , n_{CY} , and n_{XY} are the numbers of π -bonds of corresponding type, and the total number of all π -bonds $n = n_{\text{CC}} + n_{\text{CX}} + n_{\text{CY}} + n_{\text{XY}}$.

For deriving the aromaticity index ΔN proposed by Pozharskii (85KGS867) the sum of absolute values of all differences between the bond orders of n skeletal bonds including those with equal values of the orders is calculated and it is normalized with respect to the number of those differences equaling that of the dual combinations of n

$$\Delta \bar{N} = \frac{\sum |\Delta N|}{c_n^2} \quad (25)$$

When the percentage of aromaticity is to be calculated, benzene is the 100% reference structure ($\Delta \bar{N} = 0$). With the aid of the ΔN index, the aromaticity of a separate ring in a polycyclic molecule may be estimated (85KGS867).

A similar index was suggested by Bird (85T1409; 86T89; 87T4725). In this case, the variation in bond orders is described as

$$V = \frac{100}{N} \left[\sum (N - \bar{N})^2 / n \right]^{1/2} \quad (26)$$

where \bar{N} is the arithmetic mean of various bond orders and n is the number of bonds. For the D_{6h} benzene structure $V=0$, whereas in the case of the Kekule structures of five- and six-membered rings with bond alteration $V_k = 35$ and 33.3, respectively. With this notation the aromaticity index I may be represented by (85T1409)

$$I = (1 - V/V_k)100\% \quad (27)$$

When deriving the indices $\Delta \bar{N}$ and I , used to calculate the values of bond orders N from experimental data on bond lengths R , the following empirical relationship is employed:

$$N = a/R^2 - b \quad (28)$$

The constants a and b are given for various bonds in (85KGS867, 85T1409). A drawback inherent to both these indices is their inapplicability to the estimation of aromaticity of high-symmetry structures, such as 1,3,5-triazine. The values of structural indices listed in Table IV indicate, as a rule, the same trends in estimates of aromaticity of a given series of compounds. Note, however, that the $\Delta\bar{N}$ index shows furan to be 8 times less aromatic than benzene, whereas with the I index the reduction is only by 2.3. Furthermore, according to the I scale, pyridine and pyrimidine are nearly equally aromatic (86T89), but the ratio between the respective indices $\Delta\bar{N}$ shows the aromaticity of pyrimidine to be 82% that of pyridine (85KGS867). Since both indices are of the same type, such discrepancies are not admissible (90UK197) and appropriate modifications are required.

An aromaticity index has been proposed (83JOC1344) based on the magnitude of the minimal bond order in cyclic molecules. This magnitude corresponds to the weakest bond in the ring, which, in turn, sets an upper limit to the magnitude of the ring current. The bond order is defined as the weighted sum of eigenvalues of the two-center parts of the density matrix for a pair of given atoms. With the bond orders so defined, this index (ring current index, RCI) may be applied to nonplanar molecules as well. When the magnitudes of the bond orders in ethane (1.254) and ethylene (2.155) are taken as the reference points, the conjugated cyclic components are classified into aromatic (1.775–1.694), moderately aromatic (1.548–1.332), nonaromatic (1.297–1.212), moderately antiaromatic (1.176–1.140), and antiaromatic (1.042–0.98) ones. The values of this index calculated by the SINDO 1 method are presented in Table IV. The virtue of this index is that it may be applied to a wide spectrum of compounds, including excited states and unstable compounds on which no reliable experimental data on molecular geometry are available, as well as some hypothetical structures (84JOC4475; 86T417).

TABLE IV
STRUCTURAL INDICES OF AROMATICITY

Compound	$\Delta\bar{N}$ (%) (85KGS867)	I (%) (86T89)	RCI (84JOC4475)
Benzene	100	100	1.751
Pyrrole	37	59	1.463
Furan	12	43	1.430
Thiophene	45	86	—
Pyridine	82	85.7	1.731
Pyridazine	65	78.9	1.716
Pyrimidine	67	84.3	1.727
Pyrazine	75	88.8	1.739

The result obtained are, by and large, in agreement with experiment as well as with other aromaticity indices (e.g., TRE). At the same time, for certain compounds the results prove clearly unsatisfactory. Thus, pyrazole (1.463) turns out to be nonaromatic.

Some other structural criteria of aromaticity were suggested including those aiming at estimates of the stability of high-symmetry structures against distortion of different kinds, i.e., nonplanar deformation (85JA4146; 88JOC2129) or into bond-alternating forms (82ZOR1345; 85UK86).

It may be concluded, however, that in general no straightforward relationship has been disclosed between the trend toward such structural variation and the effects of cyclic electron delocalization manifesting aromaticity. For this reason, none of the above-considered structural indices, phenomenological in essence, may claim to represent a general quantitative scale of aromaticity (antiaromaticity). This would, apparently, be possible only on the condition that out of numerous factors the effect that the aromaticity (cyclic electron delocalization) exerts on the alternation of bond lengths in a given ring could be singled out and evaluated. This task is solved in a more satisfactory manner in terms of the energy criteria, whereas the structural criteria better suit the purpose of estimating quantitative variations of aromaticity in a series of molecules of the same type.

C. MAGNETIC CRITERIA

Magnetic criteria of aromaticity are based on the model of interatomic teratomic ring currents induced in conjugated cyclic molecules by external magnetic fields.

Ring currents cannot be directly determined by experimental methods. However, comparison of experimental values of magnetic susceptibilities and their exaltations and anisotropies as well as of ^1H -NMR chemical shifts with the respective data calculated from the ring current model points to the adequacy of this model for the interpretation of experimental results. The magnetic susceptibility associated with the ring current I (83BCJ1853), known as the London susceptibility, is given by

$$\chi = \frac{IS}{cH_0} \quad (29)$$

where S is the area of ring and H_0 is the value of magnetic field. For aromatic annulenes with the number of π -electrons $N = 4n + 2$ (where n is the natural number) for any value of the bond alternation negative contribution to the susceptibility takes place (diamagnetic ring current).

By contrast, in the case of antiaromatic C_NH_N molecules with $N = 4n$ the contribution is positive (paramagnetic ring current).

Calculations of the values of the London susceptibility for $(4n+2)$ - and $4n$ -membered circuits in polycyclic hydrocarbons have shown (84CPL451; 85JA298) that for the magnetic susceptibility a rule can be formulated analogous to the generalized Hückel electron count rule. Note that this rule for Hückel annulenes is opposite that for the Möbius annulenes (87CPL371). Namely, a polycyclic conjugated molecule containing only the $(4n+2)$ -membered circuits exhibits diamagnetic London susceptibility, whereas a polycyclic hydrocarbon with only the $4n$ -membered circuits will have paramagnetic London susceptibility. As opposed to the Hückel annulenes, in the corresponding Möbius annulenes the $4n$ π -electron molecules have diamagnetic susceptibilities and the $4n+2$ π -electron molecules are characterized by paramagnetic London susceptibilities (87CPL371).

The question to be answered in the first place is whether the ring current model criterion is compatible with the chief energy criterion of aromaticity and antiaromaticity. The answer will be positive if a relationship is revealed between ring currents and resonance energies.

As has been shown by Aihara (82PAC1115) the influence of a magnetic field on the total π -electron energy of a molecule manifests itself in the change of only those contributions to the magnitude of the coefficients of the characteristic polynomial $P(X)$ that are due to the presence of rings. The contributions of this category represent a monotonically decreasing function of H , which means that their values are smaller than the values of such contributions to the $P(X)$ coefficients for a field-free conjugated system. Since these contributions contain, as it were, "encoded" effects of the electron cyclic delocalization, the external magnetic field reduces the magnitude of these effects and, accordingly, of the aromatic stabilization (antiaromatic destabilization). As the acyclic reference polynomial, the energy of the reference structure stays in this case unchanged and there occur corresponding changes in the REs. Thus, by reducing the aromaticity or antiaromaticity the magnetic field destabilizes aromatic molecules and ions while stabilizing antiaromatic ones (82PAC1115; 85JA298; 86ZSK15). It was found indeed by analysis [81JA(103)5704; 82PAC1115] that for a monocyclic conjugated molecule a relationship between the RE and the London susceptibility χ exists

$$\chi \approx -RE\theta_N^2 \quad (30)$$

where

$$\theta_N = eS_N/c \quad (31)$$

Here S_N is the area of the N -membered ring.

Thus, the ring currents are directly related to the REs indicating compatibility of the model in question with the energy criterion of aromaticity. Moreover, the conclusions as to aromaticity drawn from calculated values of the ring currents are in accord with those derived from a set of experimental parameters.

All the same, the quantitative determination of the aromaticity and antiaromaticity from the ring current model may be complicated by at least two problems. First, experimentally observable values of magnetic susceptibilities and their exaltations and anisotropies as well as the ^1H -NMR chemical shifts are not necessarily determined exclusively by ring currents; hence, all other effects have to be identified and removed. Naturally, for this model to work, the contribution by the ring current must be predominant. Another problem is that the calculated results on ring current intensities for molecules from the diatropic–paratropic border area may vary qualitatively depending on the method of calculation (80PAC1541).

1. *Magnetic Susceptibility Exaltation and Anisotropy*

Since the magnetic susceptibility anisotropy $\Delta\chi$ is a characteristic attribute of aromatic molecules (66MI1; 75MI2), its value could play the role of an aromaticity index

$$\Delta\chi = \chi_{cc} - 1/2(\chi_{aa} + \chi_{bb}) \quad (32)$$

with c being the out-of-plane axis for the planar molecule (66MI1; 77JA1836).

Direct application of $\Delta\chi$ for the quantitative evaluation of aromaticity is, however, not practicable since its magnitude is not determined by ring currents only. Quite substantial effects may be played by a local contribution by the π -bond anisotropy and the anisotropy of CC and CH σ -bond magnetic susceptibilities as well as by the anisotropy due to local paramagnetic currents (for more detail, see, e.g., 66MI1).

This was found indeed to be the case of 2-pyrone and 4-pyrone, which do possess fairly large values of $\Delta\chi$ but their origin is determined mainly by local effects (69JA1991). Thus, the conclusion is obvious—the local and nonlocal contributions to $\Delta\chi$ ($\Delta\chi^{\text{local}}$ and $\Delta\chi^{\text{nonlocal}}$) must be sorted out and only the latter is to be used as an aromaticity index (73JA7961; 74TL2885).

Another quantitative characteristic of the magnetic manifestation of aromaticity is represented by the exaltation of the total magnetic susceptibility Λ (68JA811; 75MI2). For conjugated compounds, this parameter is given by the difference between χ_M and χ'_M standing, respectively, for the experimentally measured molar susceptibility and the molar susceptibility

calculated by an additive scheme:

$$\Lambda = \chi_M - \chi'_M \quad (33)$$

More precisely, Eq. (33) represents the difference between the magnetic susceptibility of a cyclic conjugated system and that of a hypothetical cyclic system with localized double bonds in which the ring current vanishes. A molecule is aromatic when $\Lambda > 0$ and antiaromatic when $\Lambda < 0$, and at $\Lambda \sim 0$ it is nonaromatic [61JCP1996; 68JA811; 75MI2; 83JMS(102)377].

Thus, the determination of aromaticity by means of Eq. (33) is analogous to the scheme for calculating the RE. Several systems of additive parameters are known for calculating χ'_M for a reference structure [56MI1; 66-AG(E)288; 75MI2].

It is on the value of Λ that the index of aromaticity ρ is based (84RRC613)

$$\rho = k \frac{n\Lambda}{S^2} \quad (34)$$

where n is the number of π -electrons, S is the area of the ring, and k is the scaling factor enabling benzene to be taken as a reference compound ($\rho = 1$ for benzene).

2. Nuclear Magnetic Resonance Chemical Shifts

The secondary field H' induced by the ring current deshields the protons lying in the molecular plane outside the ring. By contrast, the protons above and under the ring plane where the total field ($H_o + H'$) is smaller are strongly shielded. The deshielding of the outer protons and stronger shielding of the inner ones in aromatic annulenes as well as the opposite effects in antiaromatic annulenes attributable to diamagnetic or paramagnetic ring currents offer an, at first sight, attractive opportunity for devising a scale of aromaticity and antiaromaticity [75MI1; 80MI1; 84MI1; 86MI1]. (This question has been considered in detail [see 66MI1; also see 72ACR81; 80PAC1541; 83ACR298].) It should, however, be kept in mind that the value of the shielding constants σ of the nucleus A is determined by several different contributions (66MI1). They include the contributions σ_d^{AA} and σ_p^{AA} stemming from, respectively, the diamagnetic Langevin-type currents and the paramagnetic currents induced in the atom A itself. The contribution $\sum_{B \neq A} \sigma^{AB}$ is due to the diamagnetic and paramagnetic currents induced in the atoms B adjacent to atom A and the contribution $\sigma_{\text{ring curr}}^A$ comes from the interatomic ring currents:

$$\sigma = \sigma_d^{AA} + \sigma_p^{AA} + \sum_{B(\neq A)} \sigma^{AB} + \sigma_{\text{ring curr}}^A \quad (35)$$

The contributions of the first three types are practically local in character; they are close in value for two protons with similar structural environment, such as the ethylenic- and aromatic-type protons. It is only the last term in Eq. (35) that defines the values of the chemical shifts characteristic of aromatic or antiaromatic compounds.

The differences between chemical shifts for the outer and inner protons are quite sizeable; for the aromatic and the antiaromatic systems they are of opposite sign.

The effective use of these differences as a quantitative index of aromaticity in the case of annulenes and heteroannulenes is impeded by the following circumstances. The contribution by the $\sigma_{\text{ring curr}}^A$ is obscured by three other aromaticity-independent terms—see Eq. (35)—and by the fact that the ^1H -NMR spectra may depend on the temperature (72ACR81; 75MI1; 84MI1; 86MI1); furthermore, the monocyclic systems of small and medium size have no inner protons at all. Nor should one neglect the substantial contribution to deshielding of the outer protons in aromatic systems coming from the local anisotropic effects at the carbon atoms (75JA6956) due to the deviation of the electronic cloud from the spherical symmetry caused by chemical bonding (75JA6956; 87ACR152).

The role of the local effects is even more important in the case of heterocyclic molecules in which the values of chemical shifts depend on the nonuniform distribution of the electron density and on the anisotropy of the heteroatom. This may yield incorrect estimates of the relative aromaticity based on values of the chemical shifts. For example (90UK197), for pyrrole the proton signals ($\delta(2\text{H}) = 6.68$, $\delta(3\text{H}) = 6.22$) lie in a stronger field than those of furan [$\delta(2\text{H}) = 7.42$, $\delta(3\text{H}) = 6.37$], even though, according to energetic and some other criteria, pyrrole should have a greater aromaticity compared to furan (76JA4361). In the pyridine-bismabenzene series, the proton H_α signal is shifted downfield (78ACR153; 82JA5693), whereas the energies of isodesmic reactions unambiguously point to a lessening of the aromatic character in this series (88JA4204).



$\text{X} = \text{N}$ ($\delta(\text{H}_\alpha) = 8.29$), P ($\delta(\text{H}_\alpha) = 8.61$),
 As ($\delta(\text{H}_\alpha) = 9.68$), Sb ($\delta(\text{H}_\alpha) = 10.94$),
 Bi ($\delta(\text{H}_\alpha) = 13.25$),
 at $\text{X} = \text{CH}$ $\delta(\text{H}) = 7.37$

D. OTHER CRITERIA OF AROMATICITY AND ANTIAROMATICITY

The connection of the principal criteria of aromaticity considered above with the main factor of aromatic stabilization, i.e., electron cyclic delocal-

ization, can be clearly traced in most cases. Of course, the distinguishing features of aromatic and antiaromatic compounds are reflected in a larger set of physicochemical characteristics, many of which can, accordingly, serve as a basis for specific criteria of aromaticity.

Two groups of these criteria can be singled out. The first of these is in fact based on the historical interpretation of aromaticity of a compound as its propensity for undergoing substitution reactions with retention of structural type. The criteria making up this group rest on specific features that characterize the reactivity of aromatic compounds and some of them are interesting today only from the historical angle. The recently introduced criteria of the second group are rooted in the characteristic features of electron distribution in aromatic and antiaromatic compounds.

Although the criteria of these types are purely qualitative and cannot claim to evaluate quantitatively the degree of aromaticity, by and large, conclusions based on them are consistent with those obtained by means of the principal criteria and even quantitative agreement is not rare. However, their applicability is confined to a rather limited group of compounds.

1. *Retention of the Structural Type*

Since the aromaticity is defined as the stabilization due to cyclic electron (bond) delocalization, the data on thermodynamics and kinetics of various reactions leading to removal of cyclic delocalization system (or, conversely, to its formation) may in principle be used for assessing aromatic stabilization or antiaromatic destabilization.

This assessment may be based on the so-called empirical resonance energies determined from thermodynamic parameters of reactions characterized by retention of structural type or on various indices of structural stability and reactivity, such as the HOMO–LUMO energy gap.

a. *Empirical Resonance Energies.* Various approaches to the assessment of aromatic stabilization from heats of combustion or hydrogenation, the values of pK_a , and tautomeric equilibrium constants were suggested and surveyed in much detail (91H127, 91H329). In addition to aromaticity (antiaromaticity), numerous other factors are operative, so these estimates cannot measure up to the status of a quantitative approach. Still they may be quite useful in diagnosing the effects of aromatic stabilization or antiaromatic destabilization.

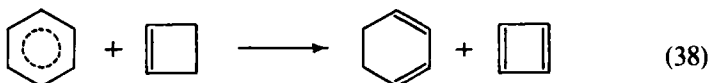
Heats of reactions. Starting with classic experiments by Kistiakowsky *et al.* (36JA146), the endothermicity of the first step, Eq. (36), of successive hydrogenation of benzene, namely, the transformation into cyclohexa-1,3-diene, unlike the exothermicity of the reactions of addition of the following hydrogen molecules, was thought to be largely associated with the loss



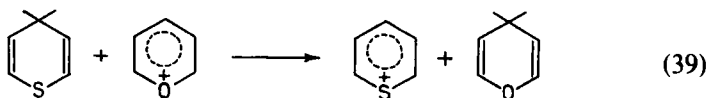
of the aromatic stabilization. For cyclobutadiene, the value of ΔH of the analogous reaction calculated by the MINDO/3 method is, by contrast, negative (75PAC767). Then ΔH Eq. (38) = ΔH Eq. (36) – ΔH Eq.



(37) = 67.5 kcal/mol can be regarded as the difference between the energies of the aromatic stabilization of benzene and the antiaromatic destabilization of cyclobutadiene, which gives for the latter the value of –41.9 kcal/mol (75PAC767). The reaction represented by Eq. (38) may



formally be considered as the dehydrogenation of cyclobutene with benzene. Here this reaction has served for comparing the aromatic and antiaromatic compounds but a reaction of this type may also be used for ascertaining the relative degree of aromaticity. An example is given by the dehydrogenation of 4*H*-thiapyran with a pyrylium cation. The equilibrium of this reaction is considerably shifted to the right, which may be regarded

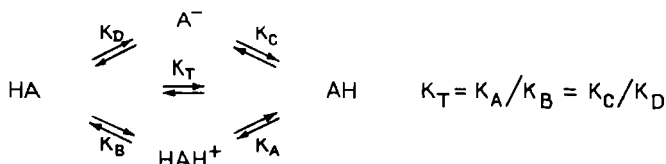


as evidence for greater aromaticity of the thiapyrylium cation over the cation of pyrylium (85KGS867).

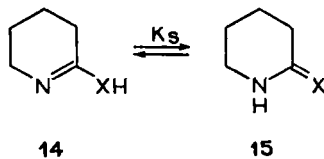
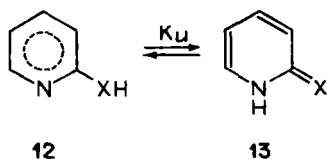
Equilibrium constants. The estimation of aromaticity may be made on the basis of equilibrium constants of reactions in which one of the interconverting forms contains a cyclic system of conjugated bonds.

Of special importance are tautomeric equilibria of two forms in which proton jumps lead to a change of the type of conjugation. Katritzky (72KGS1011; 91H329) has developed a useful approach to estimating the empirical resonance energies from the constants of tautomeric equilibria which, in their turn, are determined from the $\text{p}K_a$ values of suitable compounds properly modeling individual tautomers.

In particular, when two tautomers HA and AH form the common cation HAH^+ , the tautomeric equilibrium constants K_T can be expressed through the basicity constants K_B and K_A of these tautomers $K_T = K_A/K_B$. Since



in the equilibrium experiment the difference between the energies of two forms is determined, one can directly ascertain only the difference between aromatic stabilization energies. In this case, the influence of such effects as solvation and the difference in stability that are characteristic of the tautomeric functional groups must be taken into account. The latter effect can be included if in determining the difference between the aromatic stabilization energies (ASE) of, e.g., tautomers (12) and (13), also the system (14) \rightleftharpoons (15) is examined. Then $\text{ASE (12)} - \text{ASE (13)} = \Delta H_s - \Delta H_u$. In order to pass from the ΔG values derived from the tautomeric



equilibrium constants to the ΔH values, some approximations are introduced. In particular, one assumes $\Delta G \approx \Delta H$ or $\Delta H = 1.3 \Delta G$ (72KGS-1011). Using the above scheme, the change in the difference between the ASEs with the variation in X may be traced. Thus, 2-pyridone has a 7.5 kcal/mol smaller ASE compared to that of 2-oxypyridine ($\text{X}=\text{O}$). For $\text{X} = \text{CH}_2$, the difference between the ASEs is much greater (18 ± 3 kcal/mol) (72KGS1011).

When one of the tautomers explicitly lacks cyclic conjugation, the difference between the stabilization energies of tautomers HA and AH arising from conjugation effects including the effect of the cyclic electron delocalization may serve to evaluate the value of the ASE of the tautomer with cyclic conjugation. For more details, Elguero *et al.* [76AHC(S1)].

The estimation of aromatic stabilization (antiaromatic destabilization) energy based on thermodynamic characteristics of different reactions may yield for the same compound quite dissimilar values. As has already been pointed out, these discrepancies stem from the fact that the cyclic electron

delocalization is only one component of the overall effect with other constituents subject to considerable variations depending on the reaction type.

b. *Reactivity Indices as a Measure of Aromaticity: The HOMO–LUMO Energy Gap.* The value of the HOMO–LUMO energy separation Δ_{HL} may serve as an index of structural stability (89JOC1423) and reactivity depending on the extent to which the HOMO and LUMO take part in driving chemical reactions (88JA2092).

In general, the larger the HOMO–LUMO energy gap the lower is the tendency of the compound to react by destroying its structural type and the higher is the degree of aromaticity of the respective molecule. Such association of aromaticity with the low reactivity estimated from the Δ_{HL} value is reflected in the aromaticity criterion based on the concept of relative hardness η_r (89JA7371), which is defined as the difference between the values of the absolute hardness for a given molecule (η) and for the corresponding acyclic reference structure (η_a):

$$\eta_r = \eta - \eta_a \quad (40)$$

In the molecular orbital theory, the absolute hardness is given by (88TL4843; 89JA7371)

$$\eta = (e_{\text{LUMO}} - e_{\text{HOMO}})/2 \quad (41)$$

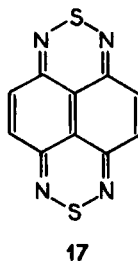
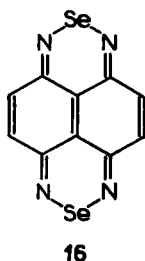
Hence, making use of the values of the corresponding roots X_i of the characteristic polynomial $P(G, X)$ and the acyclic reference polynomial $R(G, X)$ —see Eqs. (13) and (16)—the values of η and η_a can be calculated as

$$\eta = \beta(X_{\text{LUMO}} - X_{\text{HOMO}})/2 \quad (42)$$

$$\eta_a = \beta(^{\text{ac}}X_{\text{LUMO}} - ^{\text{ac}}X_{\text{HOMO}})/2 \quad (43)$$

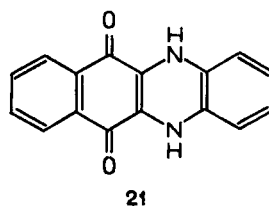
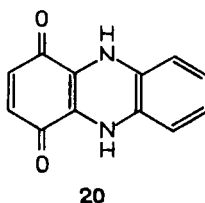
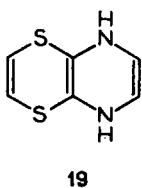
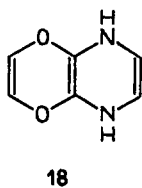
It is not surprising that the η_r values correlate well with the topological resonance energy per π -electron (TREPE). A high value of the absolute hardness, i.e., the large HOMO–LUMO energy gap, is a measure of high stability and low reactivity (89JOC1423); consequently, the corresponding η -scale reflects the lowering of the reactivity of aromatic compounds.

The values of paramagnetic ring currents are inversely proportional to the difference between the energies of the ground and the excited states (66MI1). Assuming that the energy of transition to the lowest excited state is largely determined by the HOMO–LUMO transition, one may expect that for structurally similar molecules, such as (16) and (17), the values of the paramagnetic ring currents will primarily depend on the HOMO–LUMO energy gap Δ_{HL} (79JA3306).



As has been shown by DRE (72JA4941) and TRE (78BCJ1788) calculations, aromatic (antiaromatic) character is often inverted in the lowest excited state. Therefore, for a molecule with an aromatic ground state one may expect antiaromatic destabilization of the lowest excited state and a sizeable energy gap between them. Conversely, for molecules with the antiaromatic ground state this gap will be much smaller.

This means that the antiaromatic compounds should be deeply colored; compound (17) is indeed dark-green (79JA3306), with a low energy for long-wave transitions. Evidently, this energy can qualitatively diagnose antiaromaticity (in the case of aromatic molecules); the lowest singlet transition has an energy not much different from that of the lowest transition in an olefinic molecule of the same size (71MI2). For example, in the case of molecules ((18)–(20) containing an 8 π -electron ring of 1,4-dihydropyrazine, which is an antiaromatic species [81AG(E)599], the PPP calculations show very low long-wave transition energies (83ZSK31).



2. Specific Features of the Electron Distribution

The theory of molecular structure based on the topology of molecular charge distribution, developed by Bader and co-workers (83MI2; 85ACR9), enables certain features to be revealed that are characteristic of the systems with aromatic cyclic electron delocalization. To describe the structure of a molecule, it is necessary to determine the number and kind of critical points in its electronic charge distribution, i.e., the points where for the gradient vector of the charge density the condition $\nabla\rho = 0$ is fulfilled.

The amount of the “ π -character” of a bond is determined by ellipticity (ε) of ρ_b [ρ_b is the electron density ($e \cdot A^{-3}$) at r_b] and the bond order n [83JA(105)5061; 85ACR9, 85JA3800; 88MI5; 90MI2]:

$$\varepsilon = \frac{\lambda_1}{\lambda_2} - 1 \quad (44)$$

$$n = \exp [A(\rho_b - B)] \quad (45)$$

Here, ρ_b is the bond critical point (saddle point in three dimensions, a minimum on the path of the maximum electron density). In Eq. (44), λ_1 and λ_2 are the principal curvatures perpendicular to the bond path. The parameters A and B in Eq. (45) determined using various basis sets are given in Bader *et al.* [83JA(105)5061]. Convenient parameters in the quantitative analysis of a conjugation effect are the relative π -character η (in %) of the CC formal double or single bonds determined with reference to the bond of ethylene (90MI2):

$$\eta = 100 \varepsilon (\text{CC}) / \varepsilon (\text{ethylene}) \quad (46)$$

The aromatic electron delocalization must bring the n , ε , and η values closer together for all bonds in a ring [83JA(105)5061; 85JA3800; 88MI5; 90MI2]. In benzene these values are indeed all equal for all these bonds, indicating complete delocalization ($D = 100\%$). In the prototypical antiaromatic molecule of cyclobutadiene, the π -characters of the CC bonds differ substantially (96 and 4%); D equals only 17.7%, being twice as low as that in butadiene. Thus, comparison of the ε , n , η , and D values for a given cyclic molecule with the same values for the reference acyclic structure leads to estimates of aromaticity and antiaromaticity. In the case of polycyclic molecules this approach can estimate the aromaticity of individual rings as well as that of the peripheral ring.

3. Interrelation between Various Types of Aromaticity Indices

In discussing various indices of aromaticity developed from different criteria (energetic, structural, magnetic), we noted correlations between indices based not only on one type of criteria, but also on different ones. Is, however, the interrelation among different criteria always clear-cut and convincing? Will the aromaticity inferred from, say, a magnetic criterion be confirmed by an energetic one?

Important conclusions about the interrelationship among aromaticity indices drawn from energetic, structural, and magnetic criteria stem from principal component analysis of the problem (89JA7). The scheme of principal components is given by

$$X_{ik} = \bar{X}_{ik} + \sum_{a=1}^A t_{ia} p_{ak} + e_{ik} \quad (47)$$

where X_{ik} is the mean scaled value of the experimental quantities (variables), t_{ia} are the scores, p_{ak} are the loadings, e_{ik} are the residuals, i is the chemical compound, k is the experimental measurement, and a is the principal component.

The first principal component is defined as the best summary of a linear relationship exhibited in the data. The second component is defined analogously after removing from the data the effect of the first. The principal components have definite values (t_{1i} , t_{2i} , etc., the "scores") for every compound under consideration and are taken in certain proportions (p_{1k} , p_{2k} , etc., the "loadings") for each type of characteristic.

This analysis conducted for nine compounds (benzene, pyridine, pyrimidine, pyrazine, thiophene, furan, pyrrole, pyrazole, and imidazole) has shown that 83% of the variation of 12 characteristics of the compounds (energetic, geometrical, and magnetic data) is described by the first three principal components. Relationships between various characteristics may be revealed by examining the numerical values of their principal component loadings (89JA7). According to these values, three main groups of characteristics may be identified. The first of these comprising $I_{5,6}$, ΔN , DRE, and HSRE (Table V) has large values for p_2 loadings and small-to-moderate ones for p_3 loadings. The p_1 value may be regarded as a measure of the so-called "classical aromaticity" (89JA7). The second group, orthogonal to the first, includes the magnetic indices χ_M (molar magnetic susceptibility) and Λ (exaltation) for which p_1 loadings are very small, whereas p_2 (positive value) and p_3 (negative value) are quite large (Table V). These indices describe the "magnetic" aromaticity, which is almost completely orthogonal to the "classical," which is why a correlation between them is not generally to be expected. The third comprises the

TABLE V
PRINCIPAL COMPONENT LOADINGS OBTAINED BY PRINCIPAL
COMPONENT ANALYSIS (89JA7) FOR SOME
AROMATICITY INDICES

Aromaticity indices	P_{1k}	P_{2k}	P_{3k}
$I_{5(6)}$	0.3574	-0.0088	-0.0133
ΔN	-0.3431	-0.0175	0.0274
DRE	0.3066	-0.0318	0.1675
HSRE	0.3362	-0.1203	-0.1501
χ_M	0.0508	0.4072	-0.6116
Λ	0.1075	0.4106	-0.2841
RCI	0.2645	0.1917	0.5202
I_1	0.2394	0.3613	0.0346

indices RCI and I_1 that refer to both "classical" and "magnetic" aromaticity. See also reviews under Katritzky *et al.* (91H127).

One should not forget that there are more or less certain cases of interrelationships between indices of one type and those of another, such as REs and magnetic susceptibilities due to ring currents [77JA1836; 81BCJ1245; 82PAC1115; 83JMS(102)377; 85JA298; 87CPL371].

The material presented in Section II warrants, apparently, the conclusion that the main test of aromaticity and antiaromaticity is represented by the energetic criterion realizable within the framework of various schemes for calculating resonance energies. In most cases it correlates with structural and magnetic criteria; moreover, it often accords well with a manifestation of numerous properties of compounds, which, being regarded as attributes of aromaticity, make its very concept substantially broader. Indeed, the concept of aromaticity claims an increasing number of types of compounds and requires a more and more sophisticated classification.

III. General Trends Observed in the Change of the Aromatic Character due to Heterosubstitution

A. TYPES OF HETEROATOMS

This section addresses the question how does aromatic (antiaromatic) character of compounds displaying cyclic electron delocalization change depending on the type of the heteroatom? Are conjugated heterocyclic compounds indeed characterized by a specificity, described by the term heteroaromaticity, that is in principle different from that of the corresponding hydrocarbon analogs (85KGS867)? Can there be such heterocyclic molecules possessing a greater aromaticity than that of the parent conjugated hydrocarbon?

In the search for answers it is worthwhile to examine the consequences of heterosubstitution in the case of the key representatives of the aromatic and antiaromatic classes, i.e., benzene and cyclobutadiene.

Heteroatoms may be divided into three main types X, Y, and Z depending on the number of electrons (2, 1, or 0) present in the p_z orbital of the sp^2 -hybridized atom contained in the ring (80PAC1409; 85MI2, 85MI3). Table VI lists some examples of heteroatoms of such types; also given are the so-called semiempirical aromatic electronegativity constants K_H (assuming that $R = H$) (80PAC1409; 85MI3). These are calculated by means of Eq. (48) or, in the case of atoms bound not to hydrogen but rather to the R group, from Eq. (49) using a Hammett σ_p value,

TABLE VI
SYSTEMATIZATION OF THE FIRST-ROW ATOMS THAT MAY FORM AROMATIC OR
ANTIAROMATIC RINGS^a

Type	Periodic system group:	13	14	14	15	15	16
X				—C— R (-100)	—N— (-77)	—N— R (-26)	—O— (-3)
Y		—B— R (-72)	—C— (-50)	—C— R (0)	—N— (23)	—N ⁺ — R (74)	—O ⁺ — (97)
Z		—B— R (28)	—C ⁺ — (50)	—C ⁺ — R (100)	—N ⁺ — (123)		

^a The "aromaticity electronegativity constants" for the case R = H are indicated in parentheses (80PAC1409; 85MI2).

$$k_H = 100 (0.478 Z^*/r - 1.01 - n_\pi) \quad (48a)$$

where $n_\pi = 0, 1$, or 2 for the Z-, Y-, or X-type atoms and r is the covalent radius (in Å),

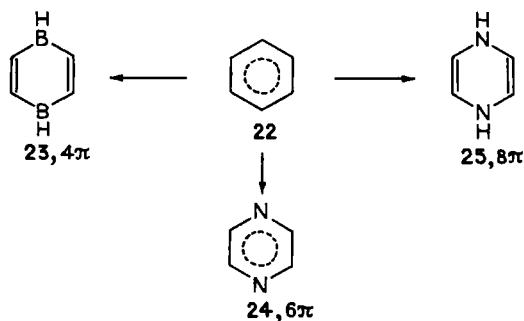
$$Z^* = Z - 0.85 n_k - 0.525 n_{L,n} - 0.175 n_{L,b} \quad (48b)$$

Here Z is the atomic number; n_k , $n_{L,n}$, and $n_{L,b}$ are the numbers of electrons in the k shell as well as of nonbonding and bonding L-electrons (80PAC1409):

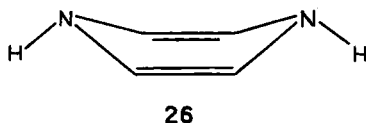
$$k_R = k_H + 20 \sigma_p \quad (49)$$

As was pointed out (80PAC1409; 85MI2) the sum k_H over all ring atoms may serve to evaluate the possibility of the existence of a given heterocyclic compound. For all heterocyclic compounds isolated or identified to date this values lies in the range -200 to $+200$ (80PAC1409).

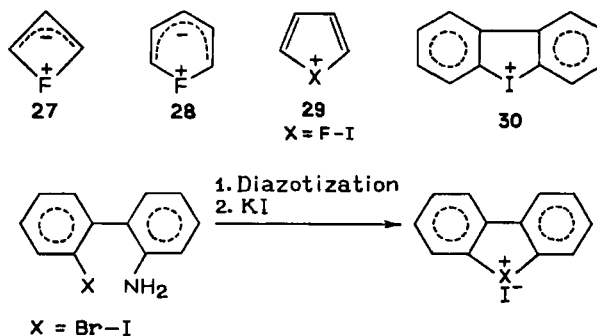
Depending on the type of the heteroatom (X, Y, or Z) that replaces the $-\text{CH}=\text{}$ group in the original hydrocarbon, heterocyclic structures may be designed with either the same number of π -electrons as in the parent molecule, or with a lesser or greater number of these. In the latter case, a change in the number of the π -electrons must reverse the aromatic (antiaromatic) character relative to the hydrocarbon analog.



Such a substitution may involve substantial changes in the structure and disturb the cyclic electron delocalization. Thus, 1,4-dihydropyrazine (**25**), as judged from X-ray data on its N-substituted derivatives [83AG(E)171] as well as from the results of MNDO [84JMS(109)277] and *ab initio* (6-31G) (88JOC2127) calculations, has a slightly bent boat structure with pyramidalized nitrogen atoms.

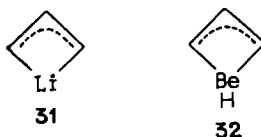


The MNDO calculations [84JST(109)277] show the C_{2v} structure (**26**) to be more stable by 8.3 kcal/mol compared to the planar D_{2h} structure. The heteroatoms given in Table VI may be supplemented by atoms of the groups 1, 2, and 17. Halogen atoms can form structures of the cyclic ylide type such as (**27**) and (**28**). In this case, a halogen atom formally supplies to the π -system three electrons, that is to say, structures (**27**) and (**28**) are, respectively, 6- and 8 π -electronic. Experimentally, these molecules have



not been detected so far, however. AM1 calculations have shown them to correspond to shallow minima on the PESs. The 6π -electron structure of cations (**29**) equally corresponds to minimum on the PES [86JCS(P2)1857; 89ZOR2033]. Some derivatives of these cations are known, e.g., structure (**30**) (84MI10).

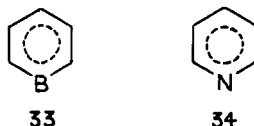
In structures (**31**) and (**32**) corresponding to minima on the PES [81JOM(219)279; 86MI6], the atoms of Li and Be accept two electrons from the π -system; i.e., they are 2π -electron molecules



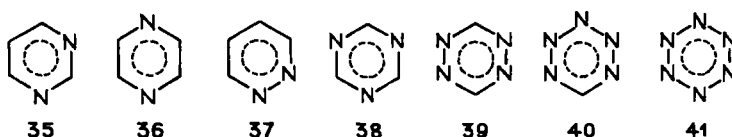
Clearly, in view of a diversity in the types of heterocyclic compounds, one may hardly expect that all the manifestations of their aromaticity (antiaromaticity) could be rationalized in terms of some simple regularities. We shall therefore attempt to trace certain characteristic trends in the dependence of the aromaticity on the type of heteroatoms, their number and positions in the molecular structure. Our reasoning will be based on the nature of the aromaticity criteria and of the electron count rules. Then turning to individual compounds, we shall add details to the picture.

B. AROMATICITY AND ANTIAROMATICITY OF HETEROCYCLIC COMPOUNDS THAT ARE π -ISOELECTRONIC WITH THE PARENT HYDROCARBON

The replacement of the $-\text{CH}=\text{}$ group in an alternant aromatic hydrocarbon with a heteroatom gives rise to the alternation of the π -electron density at the ring atoms. As a result, the aromaticity should, according to the Julg criterion, Eq. (21), be somewhat reduced. Indeed, the values of A found from the data of MNDO calculations on benzene (**22**), borabenzene (**33**), and pyridine (**34**) are, respectively, 1.0, 0.939, and 0.971. Homodesmotic stabilization energy calculations indicate (Table II) that pyridine is, in its aromatic character, only slightly inferior to benzene. The values



of the resonance energy (HSRE, TRE, CCMRE) (see Table I) point to a lessening of the aromaticity in the order benzene (**22**) > pyridine (**24**) > pyrimidine (**35**) > pyrazine (**36**); note that the change in the RE value is in this case insignificant. Nearly the same trend is observed for the structural index $\Delta\bar{N}$ (Table IV), according to which the aromaticity relative to benzene makes for (**34**) 82%, for (**35**) 67%, for (**36**) 75%, and for pyridazine (**37**) 65% (85MI1).



The aromaticity of azines is reduced relative to benzene, as is evidenced by the RCI values (83JOC1344) (Table IV) as well as by the RE values calculated from the energies of hydrogen-transfer reactions (89JA4178) (Table VII). For example, in the case of pyridine the MP3/6-31G** calculated energy of the homodesmotic reaction (50) equals -1.8 kcal/mol. Since the RE of benzene determined from the hydrogenation enthalpies is 36 kcal/mol, pyridine's RE will, accordingly, be 34.2 kcal/mol.

Thus, azines, with the exception of possibly *s*-tetrazine (**39**), have similar resonance energies (Table VII). Even though the π -density is concentrated

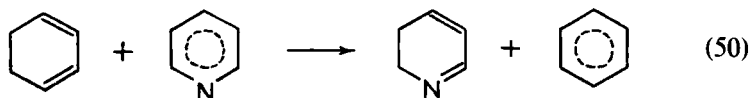
TABLE VII
AROMATICITY INDICES FOR AZINES

Compound	RCI (83JOC1344)	RE(89JA4178) ^a MP3/6-31G** //6-31G*	ΔH_{diss} (89JA4178)	
			Calc. ^b	Obs.
Benzene	1.751	36	153	143
Pyridine	1.731	34.2	117	105
Pyrazine	1.739	32.0	74	70
Pyrimidine	1.727	32.6	78	70
Pyridazine	1.716	26.1	50	50
<i>s</i> -Triazine	1.724	24.8	40	40
<i>s</i> -Tetrazine	1.735	15.3	-54	-56
Hexazine	1.792	—	-213.2 ^c	

^a Calculated from the energies of hydrogen-transfer reactions; RE and Δ_{diss} are in kcal/mol.

^b Based on MP3/6-31G**//6-31G* energy changes.

^c For hexazine the MP3/6-31G**//6-31G* dissociation energy is given without ZPVE correction. Respective values for benzene and pyridine are 165.8 and 124.8 kcal/mol.



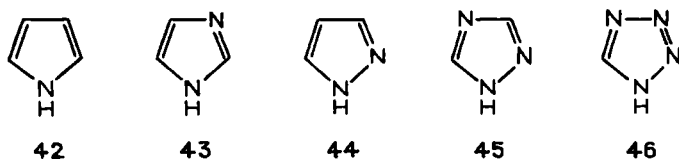
near the nitrogens, the π -density distribution per unit volume of the elements [6-31G** calculations (89JA4178)] is not changed in any significant manner when CH is replaced with N.

Relatively low RE values, compared to that of benzene, of pyridazine, *s*-triazine, and *s*-tetrazine (see Table VII) are explained, primarily, by changes in the σ -system that occur in passing from the conjugated system to the reference system, i.e., by the factors, such as the compression energy, that were noted in the discussion of the so-called empirical resonance energies.

Hexazine (**41**), which is the final product of the successive azasubstitution of benzene, possesses an even greater aromaticity than benzene—this is indicated by the values of RCI (83JOC1344) (Table VI), DRE [28.2 for (**41**), 20.0 for benzene (in kcal/mol)] (88ZOR24), and QMRE [102.5 for (**41**), 85.2 for benzene] (88IC2219). However, hexazine was isolated only in a matrix at low temperature in the process of photolysis of the complex *cis*-[Pt(N₃)₂ (PPh₃)₂] (80AG745). Its instability, in particular, with respect to the dissociation into 3N₂ (Table VII) is associated with the specificity of its σ -electronic system (Section V), e.g., with the absence of the stabilizing effect of the C—H bonds, which usually characterizes aromatic hydrocarbons (68JCP354, 88ZOR24).

Like hexazine, *s*-tetrazine (**39**) and pentazine (**40**) are thermodynamically unstable to decomposition into HCN and N₂ (see Table VII).

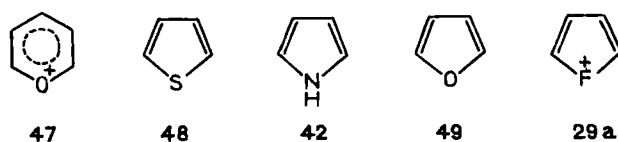
The aromaticity of azoles rises, according to the values of the structural index $\Delta\bar{N}$ (85MI1) and of HSRE (75T295), with the increase in the number of nitrogen atoms in the ring. The aromaticity relative to benzene estimated from the value of the $\Delta\bar{N}$ index is as follows: for pyrrole (**42**) 37%, for imidazole (**43**) 43%, for pyrazole (**44**) 61%, for 1,2,4-triazole (**45**) 71%, and for tetrazole (**46**) 80% (85MI1). The values of HSRE for pyrrole, imidazole, and pyrazole are 0.234, 0.251, and 0.330, respectively (in β units) (75T295).



When atoms whose electronegativities differ considerably from that of carbon are involved, it may appreciably reduce aromaticity [e.g., judging

from the structural index $\Delta\bar{N}$, the aromaticity of the pyrylium cation (47) is 43% that of benzene].

In the π -electron-excessive five-membered ring heterocycles (42), (48), (49), (29a) aromaticity decreases with an increase in the electronegativity of the heteroatom [85MI1; 86JCS(P2)1857] (Section IV,B, Tables I and VIII).



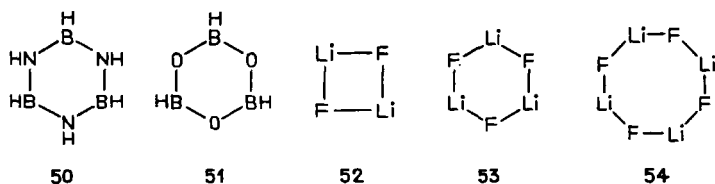
When the difference between the electronegativities of the heteroatom and the carbon is large enough, the $(4n+2)$ rule may lose its validity [71MI3; 88IJC(A)847].

Calculated values of the HSE (see Section II,A,5) (88JA4204) indicate that aromatic character is decreased with an increase in the difference between electronegativities of the neighboring atoms. For example, for the series benzene (22), *s*-triazine (38), borazine (50), and boroxine (51) the ratio between their 4-31G calculated HSE values is roughly 3 : 2 : 1 : 0

TABLE VIII
ISE AND HSE VALUES (IN kcal/mol) CALCULATED
WITH 3-21G* BASIS SET (88JA4204) FOR SOME
MONOHETEROATOMIC CYCLES

Compound	ISE ^a	HSE
Benzene	61.27	25.99
Silabenzene	46.84	17.97
Germanabenzene	46.32	16.75
Stannabenzene	42.82	12.20
Phosphabenzene	56.63	23.30
Arsabenzene	53.87	21.58
Stibabenzene	50.52	18.56
Pyrrole	43.80	5.16
Phosphole	16.49	-1.53
Arsole	16.81	-0.18
Stibole	14.33	-1.92
Furan	35.19	5.01
Thiophene	32.54	10.07
Selenophene	27.78	7.89
Tellurophene	22.19	4.31

^a Corrected for scaled ZPVE.



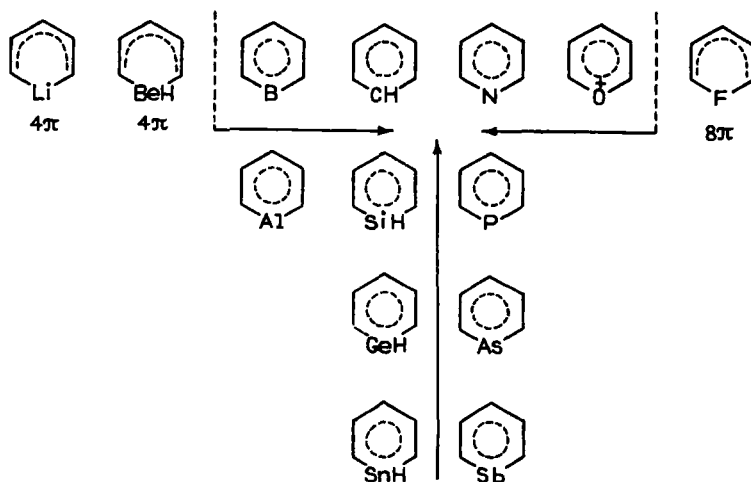
(82PAC1129). Limiting cases of the alternation of electronegativities are given by the $(\text{LiF})_n$ structures (52)–(54). Whereas the values of the energy of dissociation of $[n]$ -annulenes into n molecules of acetylene change nonmonotonically (calculated per one monomer), for the $(\text{LiF})_n$ rings these energies grow, on the contrary, monotonically (see Table IX). As one goes to main-group heteroatoms of the second and further rows, the aromatic character of heterosubstituted benzenes and pyrrole isologs $\text{C}_4\text{H}_4\text{XH}$ ($\text{X} = \text{N}, \text{P}, \text{As}, \text{Sb}$) is diminished compared to the parent hydrocarbon—this is apparent from the ISE and HSE values (see Section II,A,5) presented in Table VIII. The relative aromaticity established by the homodesmotic reaction energy as determined by MP4SDQ 6-31 G^{**} calculations (91JA3393) for the six-membered-ring $\text{X}_3\text{Y}_3\text{H}_6$ analogs of benzene is in the following order of the XY fragments $\text{CC} \gg \text{BP} \sim \text{BN} > \text{AlN}$. The above-described regularities that characterize the aromaticity of heterosubstituted benzenes are represented in Scheme 2.

Heterosubstitution in antiaromatic molecules, with the number of the π -electrons remaining unchanged, may remove the degeneracy of the incompletely filled π -levels, for example, in D_{nh} structures of antiaromatic annulenes and monocyclic conjugated ions, and lead to the stabilization of a molecule as a whole [85JA3083; 86JA3971; 88AG(E)(24)1437]. This approach represents one of the routes for obtaining stable derivatives of cyclobutadiene. Besides the introduction of electron-donating and electron-accepting substituents [76JOC3058; 88AG(E)(24)1437], the stabi-

TABLE IX
DIMERIZATION (E_2), TRIMERIZATION (E_3), AND TETRAMERIZATION (E_4) ENERGIES (IN kcal/mol) FOR ACETYLENE AND LiF CALCULATED BY MNDO AND AB INITIO METHODS

Monomer	E_2	E_3	E_4
$\text{HC}\equiv\text{CH}$	– 11.9	– 50.2	– 26.9
LiF	– 43.7(– 43.6) ^a	– 54.3(– 54.4) ^a	– 59.3(– 61.7) ^a

^a The 3-21G-calculated E_2 – E_4 energies (85JA6483) are in parentheses.



SCHEME 2

lization of a 4π -electronic four-membered ring may be achieved by the heterosubstitution to give a (55)-type system where X and Y are the atoms of different electronegativity. For a half-filled π -system, structure (55) is more stable than structure (56) (see Fig. 1) (85JA3083; 86JA3971). As distinct from (56), for (55) an effective stabilization is possible for the e_g π -MO that possesses large amplitudes at more electronegative atoms. Thus, the larger the difference between the electronegativities of the atoms X and Y, the larger is the energy splitting.



Such criteria of aromaticity as the value of ΔE (HOMO–LUMO) and the difference between the energies of the ground and the lowest singlet excited states imply that the heterosubstituted cyclobutadienes will have less antiaromaticity than the parent hydrocarbon. Indeed, according to calculations of the ISE for azetes (57)–(61) (83ZOR1353; 87ZSK28), 1,3-diazete (59) is less antiaromatic than cyclobutadiene and it is more stable than 1,2-diazete (58) (87ZSK28) (cf. Fig. 1). Also, the TRE values point to a smaller antiaromaticity of azetes relative to cyclobutadiene [88IJC(A)653]. *Ab initio* calculations of the HSE for (59) and (62)

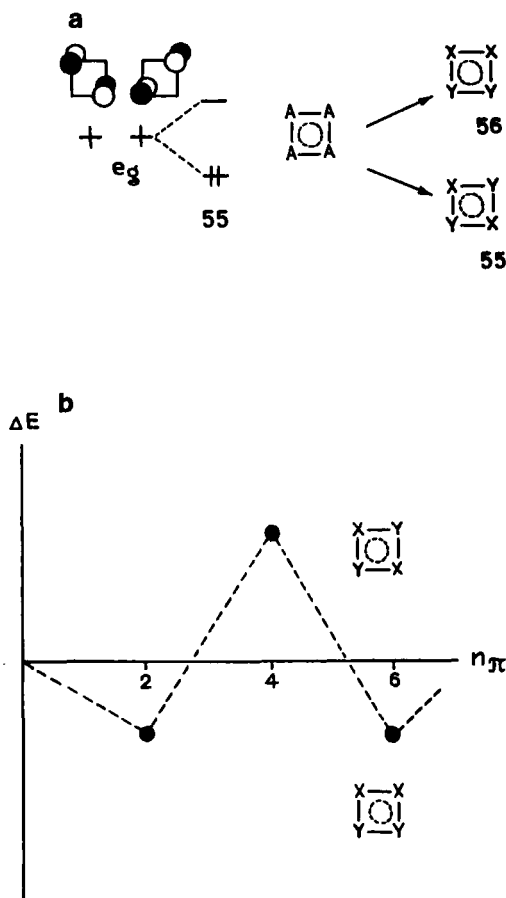
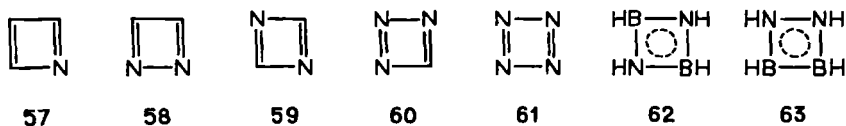


FIG. 1. (a) The lifting of degeneration of e_g π -MOs in cyclobutadiene and its heterocyclic analogs. One e_g π -MO that is localized at atoms with higher electronegativity is stabilized. This is possible for (55)-type structures in contrast to (56)-type structures (85JA3083; 86JA3971); (b) Obtained by the method of moments, the dependence of relative stability of structures (55) and (56) on the filling of π -levels (85JA3083).

(82PAC1129) show that as the difference between the electronegativities of the ring atoms grows, the degree of antiaromaticity is indeed lowered: HSE (51) = -95.0 whereas HSE (62) = -51.9 kcal/mol (4-31G) (82PAC1129).



Whereas for the D_{4h} structure of cyclobutadiene the S_0 - S_1 splitting calculated using a multireference double (MRD) CI treatment is ~ 46 kcal/mol, for (62) this value is about 89 kcal/mol [87AG(E)170], which also exceeds the value of the S_0 - S_1 splitting for (63) (Fig. 2). *Ab initio* calculations show (89JA6140) that 1,3,2,4-diazadiboretidine (62) has, unlike cyclobutadiene, a rhombic structure without bond length alternation in the ring, which is characteristic of the antiaromatic molecules.

Whereas, according to calculations of HSRE (75T295; 76JOC3058) and TRE (77JA1692) (Table I), azete (53) and 1,3-diazete (55) are less antiaromatic than cyclobutadiene, the complete azaanalog of cyclobutadiene, tetrazete (61), is characterized by a more negative value of the TRE as against cyclobutadiene [88IJC(A)653]. Thus, just as hexazine possesses greater aromaticity than benzene, so also tetrazete N_4 (61) is, judging from DRE (88ZOR24), TRE (87ZSK28), and HSE (87ZSK28) calculations,

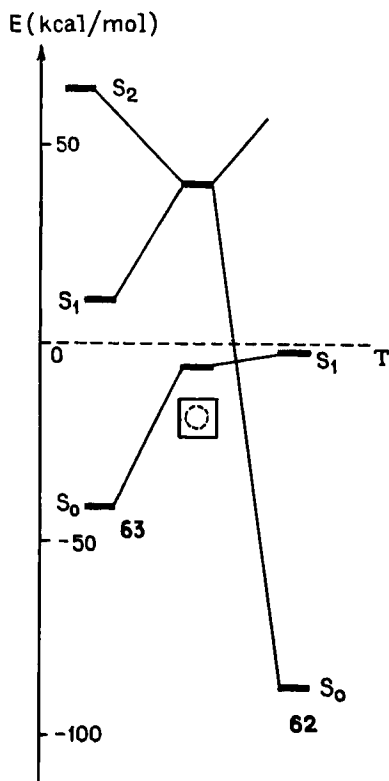


FIG. 2. The MRD CI-calculated S_0 - S_1 splitting of cyclobutadiene (D_{4h}), 1,2,3,4-diazadiborete (63), and 1,2,2,4-diazadiborete (62) (adapted from Bonacic-Koutecky *et al.* [87AG(E)170]).

more antiaromatic than cyclobutadiene. Antiaromatic monocyclic ions and antiaromatic annulenoannulenes can equally be stabilized by hetero-substitution. For example, unlike the cyclopentadienyl cation (**64**), the 1,3-diazacyclopentadienyl cation (**65**) can be isolated in the form of a stable crystalline salt, such as (**66**) [88AG(E)(24)1437] (see Fig. 3).

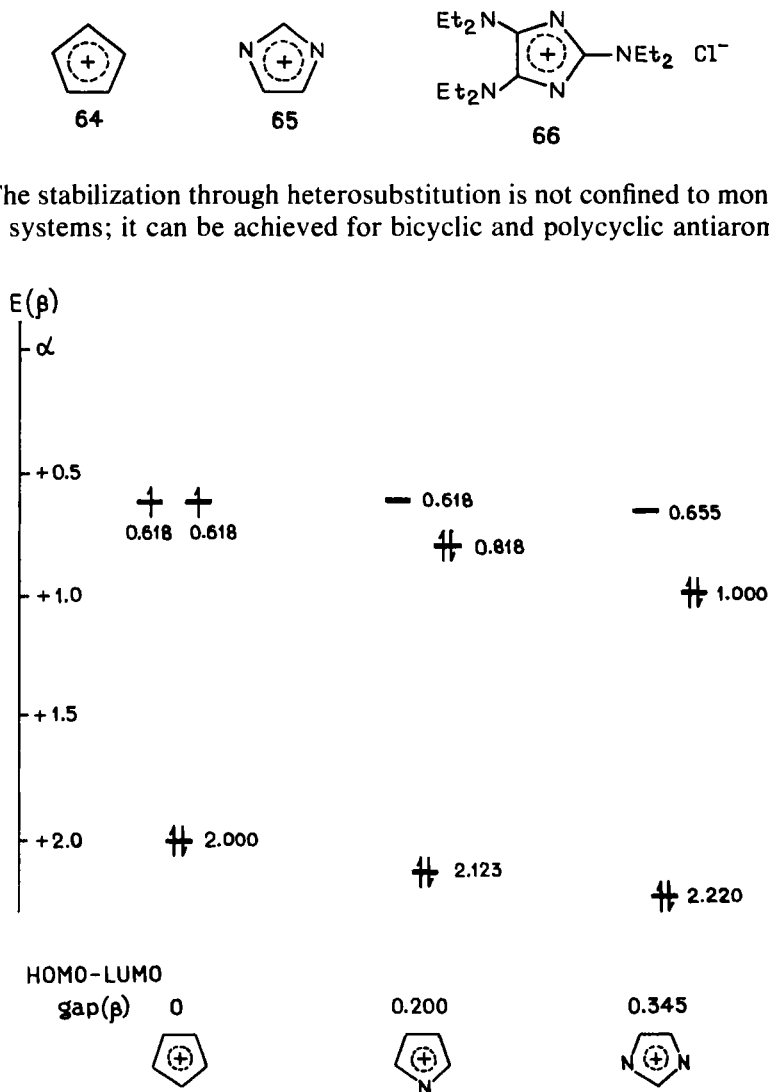
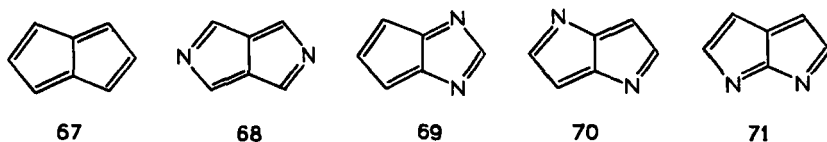


FIG. 3. HOMO-LUMO energy gaps of (aza)cyclopentadienyl cation calculated by HMO (adapted from Gompper and Wagner [88AG(E)(24)1437]).

species as well. For example, HSRE (75T295) and TRE (77JA1692) calculations indicate that 2,5-diazapentalene (**68**) is not antiaromatic, like pentalene (**67**), but rather nonaromatic: HSRE (**67**) = -0.14 , HSRE (**68**) = -0.007 , TRE (**67**) = -0.064 (in β units) (75T295; 77JA1692). These results, together with the data on the thermal stability of derivatives of (**68**) [88AG(E)(24)1437], indicate the absence of the antiaromatic destabilization in 2,5-diazapentalene.



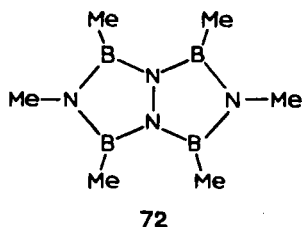
The stabilization of (**68**) provides an example of so-called topological charge stabilization [83JA(105)1979]. The maximal stabilization energy is attained in this case through insertion of heteroatoms in such sites of a conjugated hydrocarbon with nonuniform charge densities (nonalternant hydrocarbons, dications and dianions of alternant hydrocarbons) as to enable the electronegativities of heteroatoms to match the pattern of charge densities in the isoelectronic hydrocarbon species. In the case of heteroatoms with large, compared to carbon, electronegativities, the maximum stabilization is achieved when heteroatoms are introduced at sites that are characterized by the greatest charge densities in the isoelectronic conjugated hydrocarbons. Thus, in pentalene (**67**), the π -charge densities are 0.82(C1), 1.17(C2) (85JA3884). Whereas 2,5-diazapentalene (**68**) may be regarded as nonaromatic, the isomeric 1,3-diaza-, 3,6-diaza-, and 3,4-diazapentalenes (**69**)–(**71**) have TRE values (-0.376 , -0.328 , -0.336) that are even more negative than that of (**67**) (75T295).

Viewing nitrogen substitution as a perturbation of the corresponding hydrocarbon, one may derive a quantitative relationship between the RE value and those of the Coulomb integral (which, upon substitution, changes to $\Delta\alpha_i$) and the charge at the i th site. For the HSRE per π -electron (75T295)

$$\Delta \text{HSRE(PE)} = (q_i - q_i(\text{ref.})) \Delta\alpha_i \quad (51)$$

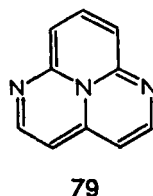
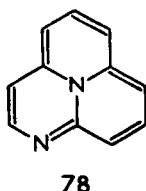
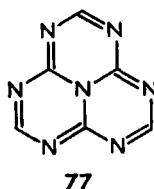
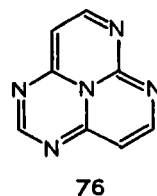
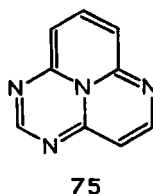
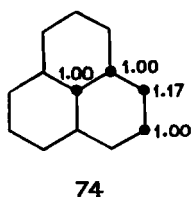
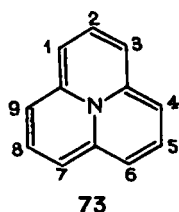
where q_i (ref.) is the value of the i th charge in the reference structure. When $q_i > 1$, nitrogen substitution must result in an increased HSRE (in β units), as is indeed exemplified by structure (**68**). Conversely, for $q_i < 1$, the value of HSRE falls as a result of the azasubstitution, as occurs in (**71**).

Whereas unsubstituted pentalene has not been obtained so far, its π -isoelectronic inorganic analog (**72**) where there occurs the topological charge stabilization has, on the contrary, been synthesized [73AG(E)576].



An example of an effective topological charge stabilization is also given by azacycl[3.3.3]azines. The cycl[3.3.3]azine (**73**), which may be regarded as a nitrogen-bridged [12]annulene [73AG(E)576], has a close-to-zero resonance energy (HSRE = 0.015 β) (72T3657); it is a highly reactive compound [76JCS(P1)341] characterized by a strong paratropic shift in the ^1H -NMR signals (72T3613, 72T3635). As judged from the values of the π -charge densities [83JA(105)1979] in the phenalenide anion (**74**) the greatest stabilization is achieved when the CH group is replaced by N atoms at the 1,3,4,6,7, and 9 positions.

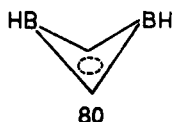
Indeed, the ^1H -NMR spectra of azacycl[3.3.3]azines (**75**) and (**76**) enable these compounds to be assigned to the aromatic class (73ACS2421). The stabilization of *s*-heptazine (tri-*s*-triazine) (**77**) (82JA5497; 84JA2805; 85JA3884) proves strong enough to make its derivatives effectively heat-stable additives in the fabrication of fireproof materials. The introduction



of only one or two additional atoms of nitrogen in (73) is insufficient to affect the stabilization always associated with qualitative changes in properties. The absence of this stabilization is exemplified by structures (78) and (79), which $^1\text{H-NMR}$ spectral data assign to the antiaromatic class (87H2757).

C. AROMATICITY AND ANTIAROMATICITY OF HETEROCYCLIC COMPOUNDS IN WHICH THE NUMBER OF π -ELECTRONS IS DIFFERENT FROM THAT IN THE PARENT HYDROCARBON

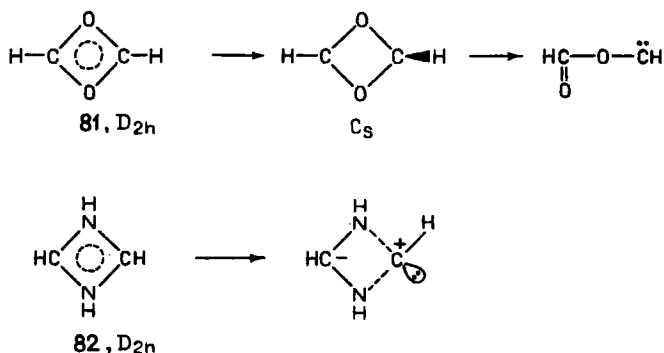
The substitution of a $-\text{CH}=\text{}$ fragment by heteroatoms of type X (2π -electrons) and Z (0π -electrons) (see Table VI) involves a change in the number of the π -electrons in a ring. 1,4-Diboracyclohexadiene (23), isoelectronic with the 4π -electron benzene dication, and 1,4-dihydropyrazine (25), isoelectronic with the 8π -electron benzene dianion, provide examples of such substituted structures. The cyclobutadiene dication is isoelectronic with 1,3-dihydro-1,3-diboretene (80), which, like the former, has a nonplanar structure. This conclusion is based on the data of an X-ray analysis of some substituted species [84AG(E)371] and of *ab initio* calculations [81MI1; 84AG(E)374].



Note that in systems of this type, particularly in small rings, the Hückel rule may prove invalid. In the case of four-membered rings this is explained by the destabilization due to 1,3-repulsions resulting from the filling of the π_2 and π_3 MOs, as has already been noted in regard to the hydrocarbons, e.g., the cyclobutadiene dianion. Thus, the 6π -electron molecules of 1,3-dioxetene (81) and 1,3-diazetine (82) should, according to the Hückel rule, be aromatic; however, as opposed to the planar 4π -electron structure of antiaromatic cyclobutadiene, these planar structures do not even correspond to minima on the PES [*ab initio* calculation (87JA6290; 90JA4155)].

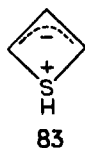
According to 6-31G* calculations (90JA4155), ring opening occurs in the cyclic structure of 1,3-diazetine without a barrier; according to Budzelaar *et al.* (87JA6290), a nonplanar $\text{HC}(\text{NH})_2^- \cdots \text{CH}^+$ complex is formed. Calculations on 1,3-dioxetene with the 3-21G basis set also point to instability with respect to the ring opening into (formyloxy) methylene (87JA6290;

90JA4155). However, when the 6-31G* basis set is employed, the C_s structure with the pyramidalized carbon atom turns out to be a local minimum on the PES (90JA4155).



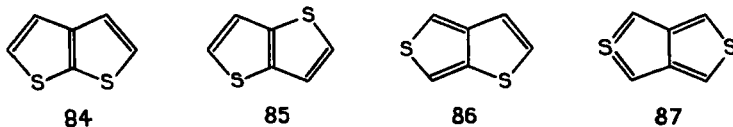
As the electronegativity of a heteroatom grows larger, the size of the p_π AO decreases, and, accordingly, the 1,3-repulsions are reduced (90JA4155). This, apparently, is one of the reasons why the 6π -electron planar rings formed by atoms that are more electronegative than carbon, such as N_4^{2-} , $(NH)_4^{2+}$, and O_4^{2+} , are less destabilized and do correspond to local minima on the respective PESs (90JA4155).

According to STO-3G calculations, the structural stability of the planar 6π -electron four-membered ring is achieved in thiacyclobutadiene (77T3061), which has a cyclic ylide-type bonding.



The approach to determine topological charge stabilization is based on the examination of the π -charge distribution in π -isoelectronic hydrocarbon species. For example, in the pentalene dianion the π -electronic densities are greatest at positions 1,3,4, and 6 [83JA(105)1979]. Accordingly, among the isomeric isoelectronic thienothiophenes (84)–(87), structures (84) and (85) are much more stable compared to (86) or (87). Structure (87) is known only in the form of 1,3,4,6-tetraphenyl-substituted derivatives (77T3203).

Such a relative stability is consistent with the RE values: for (84)–(87) the TRE values per π -electron are 0.031, 0.031, 0.026, and 0.004 (77JA1692), and the HSRE values per π -electron are 0.022 (84), 0.020 (85), and 0.015 (86) (73JA3907).



Topological charge stabilization explains the greater stability of indole (88), benzo[*b*]furan (89), and benzo[*b*]thiophene (90) compared to their positional isomers (91)–(93) when the largest π -charge densities at the 1,3-positions of the five-membered ring in the 10 π -electron indenyl anion (94) are taken into account (77JA1692). Such an order of the relative stability is consistent with the RE values (Table X).

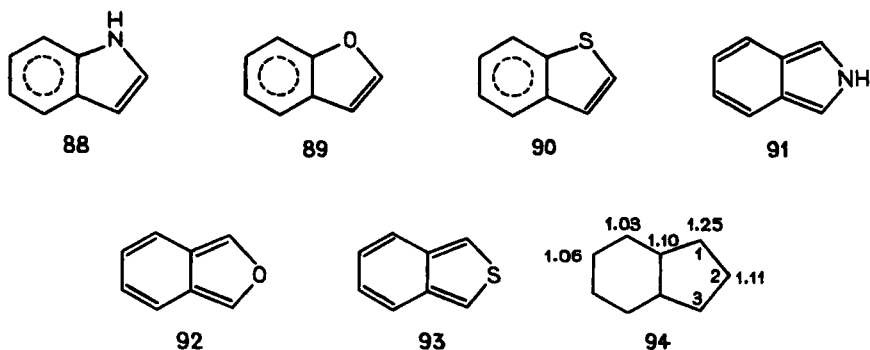
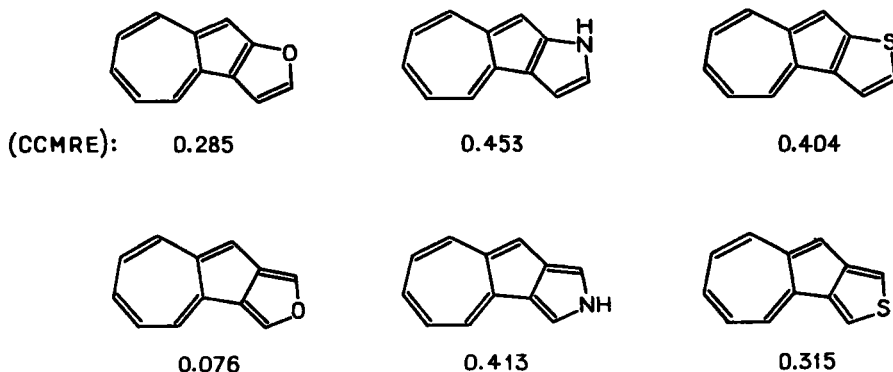


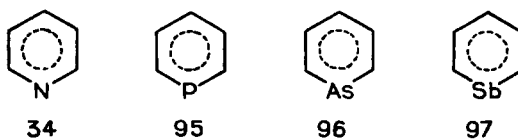
TABLE X
RESONANCE ENERGIES OF THE PAIRS OF POSITION ISOMERS (88) AND (91), (89) AND (92), (90) AND (93)

Isomers	TRE (β) (77JA1692)	HSRE (β) (72T3657, 73JA3907)	CCMRE (eV) (88CCC2024)
88	0.38	0.47	—
91	0.32	0.29	—
89	0.27	0.36	—
92	0.11	0.02	—
90	0.35	0.44	1.050
93	0.29	0.25	0.362

The ratio between the values of the TRE or between those of the HSRE for the isomer pairs (88)–(93) is analogous to that between the values of the CCMRE (given in eV under the structural formulae) for the positional isomers of azulenofurans, azulenopyrroles, and azulenothiophenes (87H2025).



We next consider how the above-described regularities of the changes in the aromaticity of the conjugated heterocyclic compounds are reflected in concrete electronic–structural characteristics. We start with derivatives of annulenes and monocyclic conjugated ions containing one heteroatom of an element of the first row of the Periodic Table. To reveal the trends in the changes of the aromatic or antiaromatic character in compounds containing heteroatoms of the elements of the same group, one may compare some series of such compounds, for example,



Of particular interest are compounds, such as sila-, germa-, and stannabenzenes (see Scheme 2), that are formed by group 14 elements (the analogs of carbon). They will be discussed in a detailed fashion (Section VI). Attention will also be given to manifestations of aromaticity in polyheterocyclic compounds in the series (35)–(41) and (57)–(61).

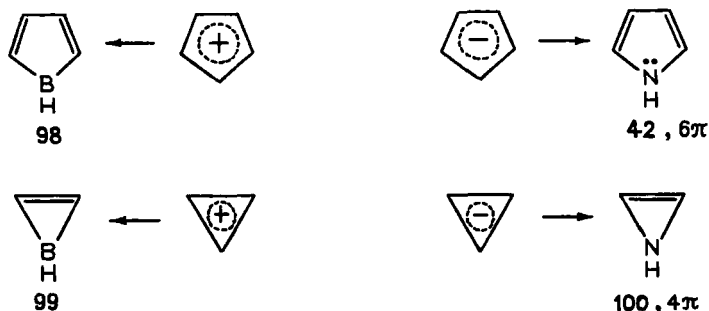
The scheme for treating these subjects is as follows. We compare typical aromatic and antiaromatic compounds. Similar to the comparison between benzene and cyclobutadiene, we concern ourselves here with pyridine (34) and azete (57). Such an approach provides, apart from other advantages,

an opportunity for direct comparison between a conjugated cyclic hydrocarbon and the corresponding heterocyclic compound.

IV. Heterocyclic Analogs of Annulenes and Monocyclic Conjugated Ions

A. HETEROCYCLIC COMPOUNDS CONTAINING ONE HETEROATOM WITH THE SAME NUMBER OF π -ELECTRONS AS IN THE PARENT HYDROCARBON

The title compounds may be classified into two groups, viz., the hetero-substituted annulenes containing a type Y heteroatom, for example, pyridine and azete, and the derivatives of monocyclic conjugated ions with heteroatoms of type X (two π -electrons) or Z (zero π -electrons) (Table VI), such as pyrrole (42)—borole (98) or borirene (99)—2-azirine (100).



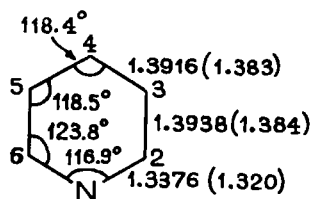
First we turn to typical representatives of heteroderivatives of annulenes, namely, the heterosubstituted benzenes and cyclobutadienes.

1. Monoheterosubstituted Benzenes and Cyclobutadienes

The replacement of a $-\text{CH}=\text{}$ group in benzene and cyclobutadiene by a heteroatom of type Y (one π -electron) with a greater p_π -orbital electronegativity than that of the carbon atom leads, respectively, to such heterocycles as pyridine and azete. A boron atom (type Z), whose p_π -orbital electronegativity is correspondingly lower, replaces $-\text{CH}=\text{}$ in the parent hydrocarbons to give borabenzene and boracyclobutadiene (62JA540; 88JCE34).

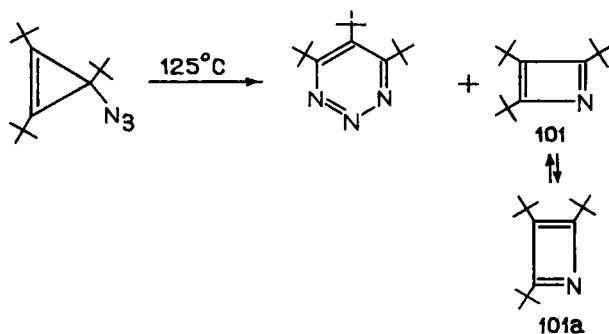
a. *Pyridine and Azete.* It has already been noted that pyridine differs insignificantly from benzene in regard to aromaticity; this conclusion rests

on energetic, structural, and magnetic criteria. Furthermore, according to microwave spectral data (77JST1), the lengths of the carbon-carbon bonds in pyridine are close to those in benzene [bond lengths are given in brackets (in Å) calculated with the 6-31G** basis set] (86MI5; also see 89KGS1587).



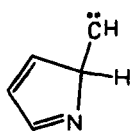
In pyridine the carbon atoms are electron-deficient so it and other heterocycles containing pyridine-type nitrogen atoms are assigned to the π -deficient species (85KGS867). According to 6-31G** calculations (89JA4178), the π -electron population in pyridine amounts to 1.426 at the nitrogen atom, 0.787 at C2, 1.029 at C3, and 0.942 at C4 atoms. As pointed out above, with this charge alternation taken into account, the aromaticity index *A* is reduced.

Like cyclobutadiene, azete (57) is characterized by bond length alternation [$R(C-N) = 1.578$, $R(C=N) = 1.274$, $R(C-C) = 1.555$, $R(C=C) = 1.321$ Å; 4-31G calculations (89JA6140); see also previous MINDO/3 and MNDO calculations (80MI2; 87ZSK28)]. Its rectangular ground state structure has been identified by ^1H - and ^{13}C -NMR spectral data of tri-*tert*-butylazete (**101**) obtained in the form of reddish-brown needles (mp 37°C) by heating azide to 125°C in the absence of solvent [86AG(E)842].

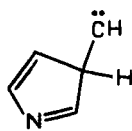


The ^1H - and ^{13}C -NMR study [86AG(E)842] shows that a rapid valence isomerization (**101**) \rightleftharpoons (**101a**) takes place. For azete, the activation barrier of the automerization via a C_{2v} transition state is 12.1 (MINDO/3) (80MI2),

14.7 kcal/mol (MNDO) (87ZSK28). By contrast, pyridine, an aromatic compound like benzene, is not likely to be susceptible to thermal automerization. Indeed, according to MINDO/3 calculations (89DOK358), such an automerization of pyridine may be realized through 1,2-CH shift with carbene structures (102) and (102a) shown below, being the transition states of conceivable routes. But the activation barriers amount in this case to ~ 100 kcal/mol.

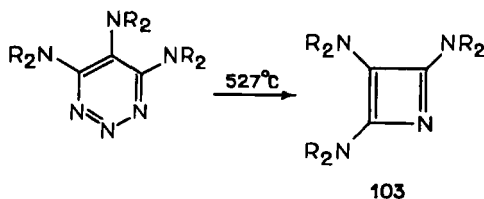


102



102a

Unlike pyridine (85MI1), tri-*tert*-butylazete (101) has, as judged from its reactivity, olefinic character [88AG(E)(27)272]. As in the case of cyclobutadiene, the push-pull substitution [69CC240; 88AG(E)(24)1437] promotes the stabilization of azete, as has been demonstrated by the isolation of the first thermodynamically stable substituted azete, tris(dimethylamino)azete (103) [73AG(E)847].

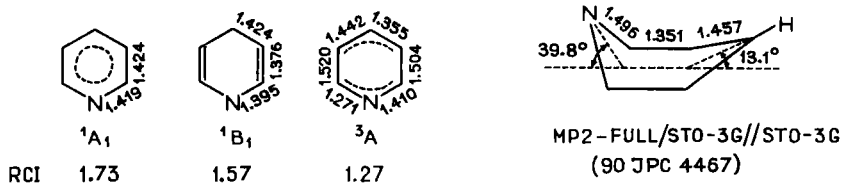


103

According to MINDO/2 calculations [73AG(E)848], (103) has a rhombic structure without bond alternation.

Whereas in the case of pyridine the lowest excited singlet 1B_1 state ($n \rightarrow \pi^*$ excitation) has, according to experimental evidence (67JSP125), an energy 99 kcal/mol too high compared to a C_{2v} structure of the ground state. The lowest excited 1B_1 state of azete (C_{2v} structure) is higher in energy by a mere 7.4 kcal/mol than the C_s structure of the ground state [4-31G CI calculations (89JA6140)]. Whereas for the structure of the lowest excited singlet 1B_1 state of azete bond alternation is not a characteristic (C_{2v} structure), the same state of pyridine has a structure with appreciable bond length alternation [SINDO1 calculations (83MI4)]. The lowest triplet 3B_1 state of azete has a planar C_{2v} structure without bond length alternation; its energy is higher by 18.0 kcal/mol than that of the ground state C_s ,

structure (4-31G) (89JA6140). By contrast, according to MP2-FULL/STO-3G (90JPC4467) and SINDO1 (83MI4) calculations, the lowest triplet state of pyridine has a nonplanar structure [boat form, double-minimum potential (90JPC4467)] with bond alternation. Judging from experimental data of adiabatic excitations (see 67JSP125, and references cited there), its relative energy is 85 kcal/mol compared to the ground state structure. SINDO1-calculated bond lengths (83MI4) are given below in angstroms for the 1A_1 (ground), 1B_1 , and 3A (excited) states. For the structure of the lowest triplet state, the geometrical parameters optimized by MP2-FULL/STO-3G calculations (90JPC4467) are also shown:

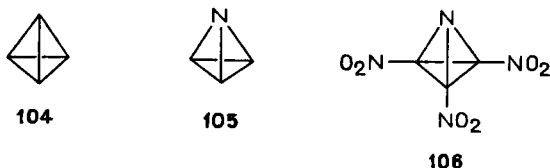


According to structural criteria, in particular, to the SINDO1-calculated (90JPC4467) values of RCI, the excited states of pyridine, as distinct from the ground state, do not possess aromatic character. This finding confirms the aromaticity \rightleftharpoons antiaromaticity (nonaromaticity) inversion in the excited state relative to the ground state.

The valence isomer of azete, azatetrahedrane (**105**), has an energy higher by 20 (MINDO/3) (80MI2), 41.2 (MNDO) (87ZSK28), 44.6 kcal/mol (4-31G) (80MI2) compared to azete. According to MP2/6-31G*//MP2/6-31G* calculations [89CPL(159)27, 89JPC588], in structure (**105**) $R(CC) = 1.442$, $R(CN) = 1.498$ Å. Comparison between the bond orders in tetrahedrane (**104**) and azatetrahedrane (**105**), calculated by [89CPL(159)27],

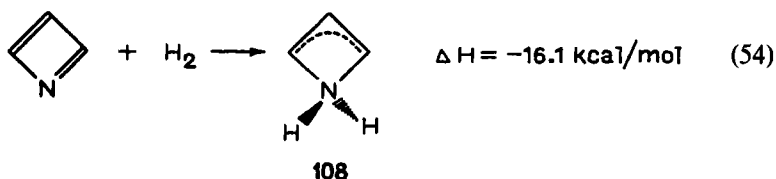
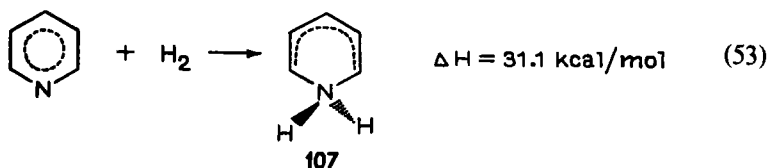
$$\text{bond order} = 0.55747 (k/R_e)^{1/2} \quad (52)$$

where k is the force constant of the bond, in mdyne/Å, and R is its equilibrium length in angstroms indicates the higher strength of the CC bonds in (**105**). Additional strengthening of the CC bonds can be achieved by the introduction of the strongly electron-withdrawing nitro group (**106**) (89JPC4742).

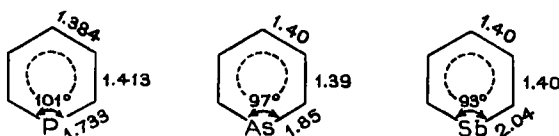


A decrease in the strain energy of (105) relative to (104) is also found in 6-31G**/3-21G calculations (86ZSK151); respective values determined from the isodesmic bond separation reactions are 113.3 and 135.0 kcal/mol.

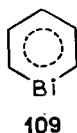
The aromaticity of pyridine and antiaromaticity of azete may be compared on the basis of the enthalpies of reactions (53) and (54). Both in structure (107) that corresponds to a minimum on the PES (unpublished results) and is an analog of the experimentally known λ^5 -phosphorine (82ACR58) and in structure (108) a tetracoordinate nitrogen atom disturbs cyclic π -delocalization. In contrast to pyridine—Eq. (53)—the corresponding reaction for azete—Eq. (54)—is according to our AM1 calculations exothermic.



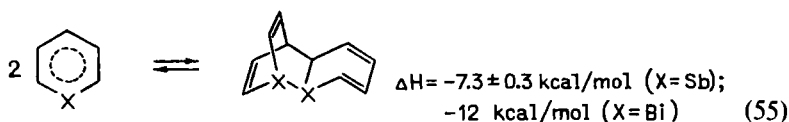
In the series of group 15 heterobenzenes 34, (95)–(97), aromatic character is diminished, albeit insignificantly, as indicated by energetic (Table VIII) and magnetic criteria (77PS77; 78ACR153; 82JA5693; 88JA4204). According to electron-diffraction and microwave data (78ACR153) and *ab initio* computational results (88JA4204; 89MI4) molecules (95)–(97) have planar structures with the CC bond lengths close to those in benzene.



The value of the C—P bond ellipticity ε calculated for phosphabenzene with the 6-31G* basis set to be 0.2558 (89MI4) exceeds that of the P—C bond in phosphine CH_3PH_2 (0.1457), which points to a somewhat double-bond character of the CP bond in (95).

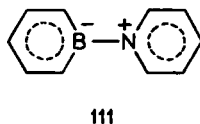
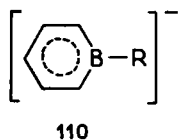


Stibabenzene (97) and bismabenzene (109) are readily dimerized (82JA5693).

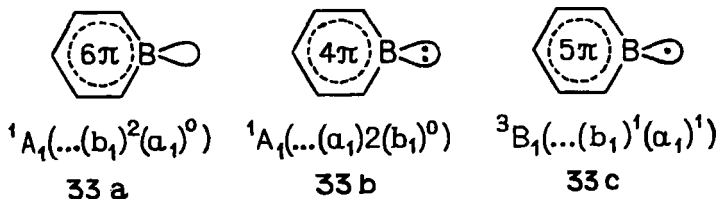


For structures (105) and (106), such a dimerization has not been detected. Low ΔH values for the (55) dimerization reflect the lessening of aromatic character of (107) and (109) compared to (34), (105), and (106) (8JA5693).

b. *Borabenzene and Boracyclobutadiene.* The HSE of borabenzene (33) is equal to 19.2 kcal/mol (6-31G*) (89MI6), whereas for benzene and pyridine it is, respectively, 24.7 and 25.4 kcal/mol. Hence the aromatic character of borabenzene is less pronounced relative to benzene and pyridine. Unsubstituted borabenzene has not been prepared (86PAC95), but a number of complexes, such as (110) and (111), are known (78JCE497;

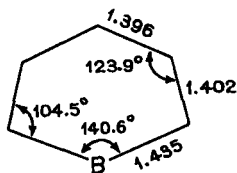


86MI9). Particularly striking is the manifestation of the decrease in aromaticity in borabenzene compared to benzene. This is explained by the specific fact that in the case of borabenzene, owing to the presence of an electron hole at the boron atom, two closed-shell electronic configurations, . . . $(b)^2(a_1)^0$ and . . . $(a_1)^2(b_1)^0$, are possible as well as one open-shell configuration, . . . $(b_1)^1(a_1)^1$. If the energy of aromatic stabilization of the 6π -electron structure (33a) turns out to be insignificant, structures of the 3B_1 state (33a) and 1A_1 state (33b) should be able to compete with it in regard to relative stability. Calculations (MNDO) have shown that the

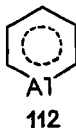


triplet 3B_1 state structure (33c) and the 4π -electron structure (33b) have energy higher by 24.7 [84ZN(A)678] and 68.9 (our data) kcal/mol than that of structure (33a); i.e., the energy difference between the lowest excited triplet state and the ground state turns out much smaller than in the case of benzene.

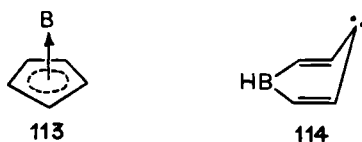
According to X-ray data on the pyridine–borabenzene complex (111) (85CB1644), the CC bond lengths in the borabenzene ring are close to those in benzene. This finding is in agreement with the 6-31G* calculation results (89MI6) (see also the data of 4-31G calculations [87ZN(A)352].



As shown, for example, by calculations of the structural index *A*, the aromaticity of alumobenzene (112) is still lower than that in borabenzene. Calculations (MNDO) have shown the ground state of this molecule to be, in contrast to benzene, triplet (3B_1). Even so, the 6π -electron structure of (112) is more stable than the 4π -electronic one. However, the difference between their energies (36.6 kcal/mol) is nearly twice as small as that for the corresponding structures of borabenzene.



The isomers (**113**) and (**114**) of borabenzene have higher energies than the borabenzene structure (**33a**) [MNDO calculations (69CC240), see Table XI]. [Structure (**113**) satisfies the 8e rule (87MI2) and corresponds to a minimum on the PES; hence it may be assigned to three-dimensional aromatic structures.]



One may reliably assume that the elusive nature of borabenzene cannot be attributed to insufficient aromaticity which, according to HSE values, amounts to 78% of benzene's aromaticity. Rather, it will be explained by high reactivity due to the σ -acceptor properties of a low-lying σ^* -MO. The stabilization of borabenzene is indeed achieved through formation of complexes with σ -donors. Note that, apart from pyridine, even dinitrogen may act as a σ -donor [88AG(E)(27)295].

TABLE XI
RELATIVE ENERGIES (IN kcal/mol) OF
BORABENZENE [1A_1 (**33a**), 3B_1 (**33b**) AND 2 1A_1 (**33b**)
STATES] AND ITS ISOMERS (**113**) AND (**114**), AS WELL
AS RELATIVE ENERGIES OF BORACYCLOBUTADIENE
STRUCTURES (**119a**)–(**119e**) AND ITS ISOMERS
(**120**)–(**122**)^a

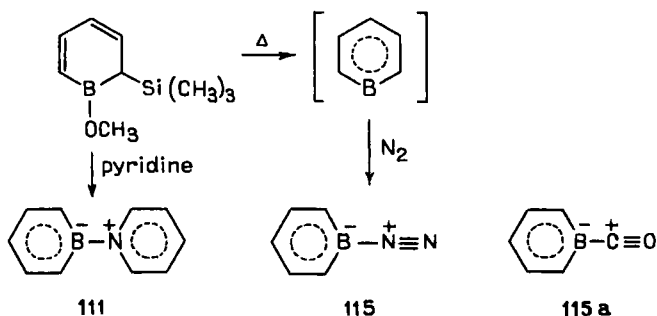
C_5H_5B		C_3H_3B	
Structure	E_{rel}	Structure	E_{rel}
33a	0	119a 1A_1 (C_{2v})	0
33b	68.9	119b 3A_2 (C_{2v})	–20.0
33c	24.7	119c 1A_1 (C_{2v})	–18.4
113	42.0	119d 1A_1 (C_{2v})	–1.6
114	43.1	119e 1A_1 (C_s)	–10.0
		120 1A	–8.5
		121 3A_2	39.4
		122 1E	57.6

^a Calculated using the MNDO method (unpublished results).

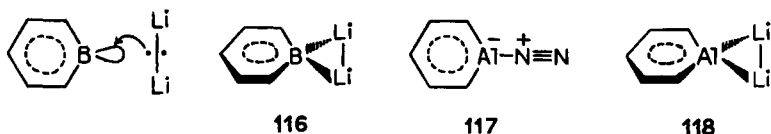
The MNDO-calculated enthalpies of reactions of borabenzene with pyridine and dinitrogen are, respectively, -39.6 and -25.2 kcal/mol [88AG(E)(27)295].

Bader population analysis has shown (90JA1707) that the complex (115) is primarily formed through the σ -donation from the nonbonding σ -orbital of N_2 to the low-lying vacant σ^* -orbital of borabenzene supplemented by the π -back-donation from the b_1 π -orbital of borabenzene to the vacant π^* -orbital of N_2 .

Also, the borabenzene adduct with CO (115a) proves stable. According to MP2/6-31G*//6-31G* calculations (90JA1707), the energies of complexes (115) and (115a) are lower by, respectively, 16.4 and 39.4 kcal/mol than the sum of the energies of free molecules.

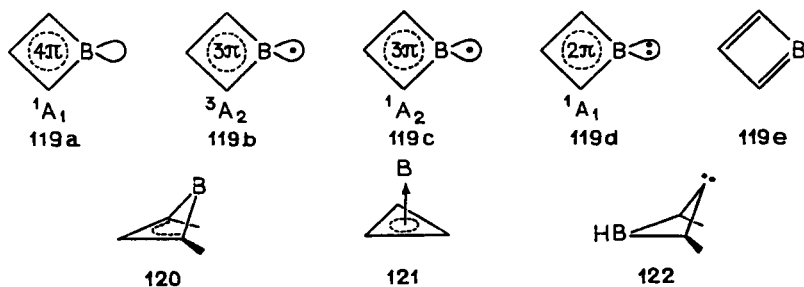


Reaction of borabenzene with Li_2 gives structure (116) in which the tetracoordinate boron atom has a planar bond configuration [MNDO (90ZOR210)]. A structure with the tetrahedral bond configuration has an energy higher by 9.6 kcal/mol compared to structure (116) and represents a transition state in the topomerization of the latter.



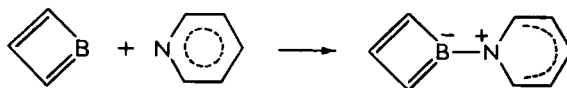
As is apparent from MNDO calculations, structures (117) and (118), which are similar to (115) and (116), can also be formed with alumobenzene.

Structures analogous to (33a)–(33c) are also possible in the case of boracyclobutadiene. However, in this case the antiaromatic 4π -electron structure (119a) has a higher energy compared to structures (119b) and (119c) of the 3A_2 and 1A_2 electron states that correspond to minima on the PES (Table XI).



The C_s structure (**119e**) with bond alternation possesses a lower energy than C_{2v} structure (**119a**). The 2π -electron structure (**119d**) is slightly more stable than the 4π -electron C_{2v} structure (**119a**); however, its energy is higher relative to that of the nonplanar C_s structure (**120**) (see Table XI).

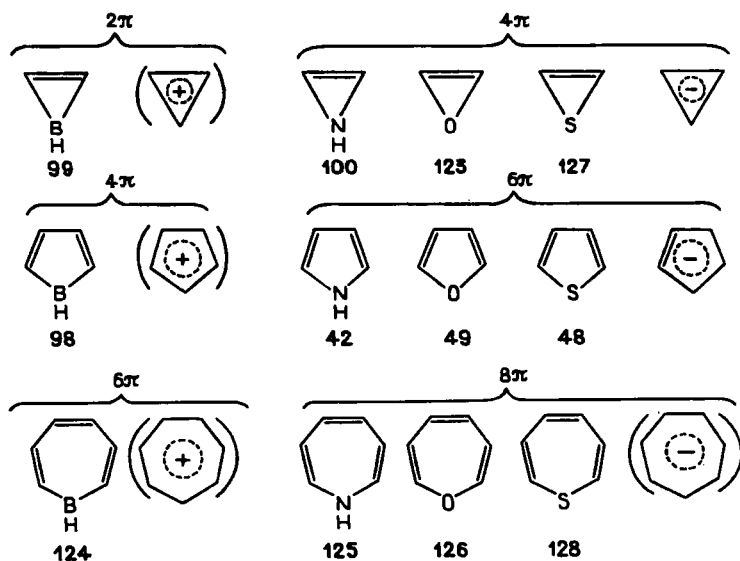
Boratetrahedrane (**121**) that has the triplet 3A_2 ground state and the carbene C_s structure (**122**) possess higher energies than that of structure (**119e**). Similar to borabenzene, the stabilization of boracyclobutadiene (**119e**) can be achieved through the formation of a complex with pyridine.



2. Heterocycles, Containing One Heteroatom, π -Isoelectronic with the Parent Conjugated Hydrocarbon Ions

Before turning to manifestations of aromaticity or antiaromaticity, relative stability, geometry, and other characteristics of the molecules represented in Scheme 3, we wish to treat in some detail certain regularities in changes of aromaticity depending on the type of heteroatom as well as the relationship between the geometry of a given molecule and its aromatic (or antiaromatic) character.

a. *Aromaticity in the Series of Pyrrole, Furan, Thiophene.* As already noted, the aromaticity of the best-studied aromatic heterocycles pyrrole (**42**), furan (**49**), and thiophene (**48**) decreases in the order (**48**) > (**42**) > (**49**) [see Tables I, X, XII (76JA4361; 85KGS867; 88JA4204)]. Results presented in Bernardi *et al.* [88JMS(163)173] reveal the "anatomy" of the aromaticity of these compounds. The π -electron delocalization energies were determined by calculating the energy effects associated with fragment π -orbital interactions using the quantitative PMO treatment. To



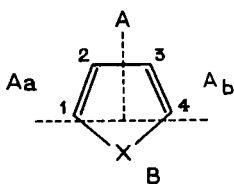
SCHEME 3

TABLE XII
 TOPOLOGICAL RESONANCE ENERGIES (TRE), HESS-SCHAAD RESONANCE ENERGIES (HSRE), AND RING CURRENT INDICES (RCI)^a

Compounds	TRE (77JA1692, our results)	HSRE (72T3657; 73JA3907)	RCI (83JOC1344; 84JOC4475)
99	0.165	—	1.614
98	-0.080	—	1.140
124	0.026	—	—
100	-0.129	—	1.031
42	0.040	0.039	1.463
125	-0.029	-0.036	—
123	-0.109	—	1.030
49	0.007	0.007	1.430
126	-0.004	-0.006	—
127	-0.107	-0.114	—
48	0.033	0.032	—
128	-0.023	-0.029	—

^a TRE and HSRE are in β units.

that end, the heterocyclic system was divided into fragments, as shown in Scheme 4.



SCHEME 4

The interaction energy for the union of the constituent fragments is evaluated using

$$\Delta E = \sum \Delta E_{ij}^4 + \sum \Delta E_{ij}^2 \quad (56)$$

where $\sum \Delta E_{ij}^4$ represents the four-electron destabilization energy determined by the interaction between the doubly occupied orbitals Φ_i and Φ_j , whereas ΔE_{ij}^2 is the two-electron stabilization energy dictated by the interaction between a doubly occupied orbital Φ_i and a vacant orbital Φ_j' (for detail, see, e.g., 87MI2, and the literature cited there). First the interaction between the two ethylenic fragments A_a and A_b was examined. The corresponding stabilization and destabilization energies obtained for the experimental geometry of the molecules in question are given in Table XIII. According to these values, the destabilization effect $\Delta E_{\pi\pi}^4$ is lowered from furan to thiophene where the $C_1C_2C_3$ angle is greater than that in furan. Then an interaction was considered between the butadiene fragment and the X fragment ($X = O, NH, S$; for the reference benzene molecule $X =$ ethylene fragment) (see Fig. 4). For all the heterocycles under consideration, the overall effect $[\sum \Delta E]_{II}$ is stabilizing.

The following important conclusions can be drawn from the above results [88JST(163)173]. First, the values of $[\sum \Delta E]_{II}$ are nearly equal for furan and pyrrole; hence the correct aromaticity trend can be ascertained only if the $[\sum \Delta E]_I$ contributions are also taken into account. Thus, the relative aromatic character of the compounds under discussion is determined by the sum of the stabilizing effects of the two electron interactions. These are the stabilization energy $\Delta E_{n\Phi_j}^2$, referring to the interaction be-

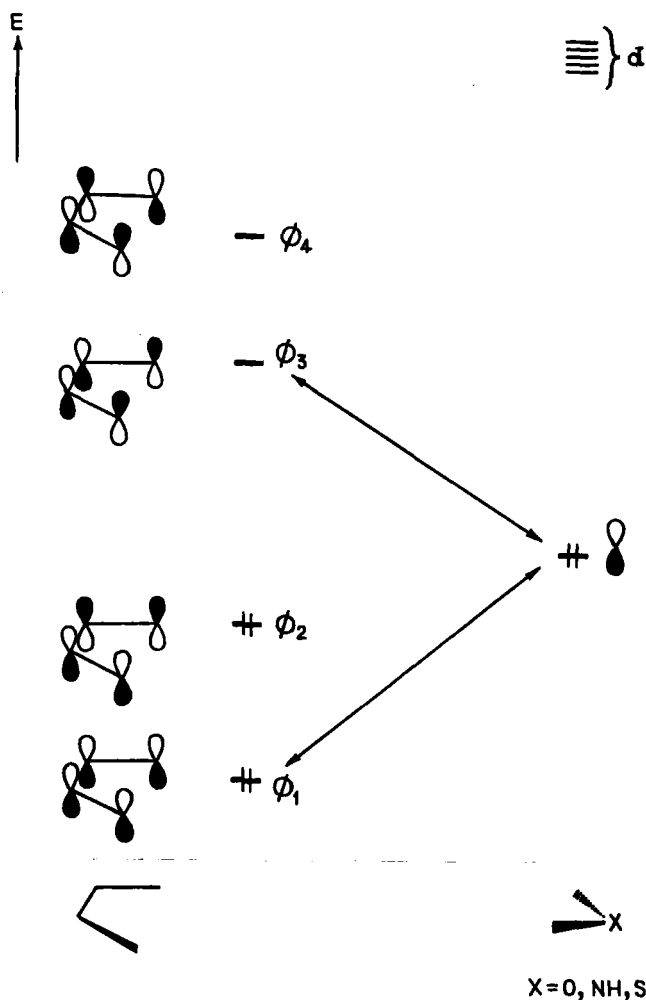


FIG. 4. Diagram of the interactions between the butadiene fragment and the X-fragment ($X=O, NH, S$) (adapted from Disch and Schulman [88CPL(152)402]).

tween butadiene and the X fragment (76JA4361), and $\Delta E_{\pi\pi}^2$, referring to the interaction between two ethylene fragments. This stabilization effect is stronger for pyrrole than for furan, whereas in the case of furan the destabilizing effect of ΔE_{no}^4 is greater than that for pyrrole (Table XIII). The total values of $[\Delta E] = [\Delta E]_I + [\Delta E]_{II}$ are consistent with the values of the TRE, HSRE, RCI, ISE, and HSE (Tables I, VIII, XII). Second, the difference in aromaticity between pyrrole and furan, on the one hand,

TABLE XIII
STABILIZATION (ΔE_{ij}^2) AND DESTABILIZATION (ΔE_{ij}^4) ENERGIES (IN
kcal/mol) OBTAINED FOR FURAN, PYRROLE, THIOPHENE, AND BENZENE
AT THE STO-3G (STO-3G* FOR THIOPHENE) COMPUTATIONAL
LEVEL [88JST(163)173]

	Furan	Pyrrrole	Thiophene	Benzene
Interactions between fragments A _a and A _b				
$\Delta E_{\pi\pi}^4$	28.27	28.33	25.09	28.96
$\Delta E_{\pi\pi}^{2*}$	-13.08	-16.13	-16.13	-29.29
$\left[\sum \Delta E \right]$	2.11	-3.93	-7.17	-29.62
Interactions between fragments A and B ^a				
$\Delta E_{n\sigma}^4$	44.54	55.57	30.66	31.03
$\Delta E_{n\sigma}^{2*}$	-103.95	-114.67	-95.71	-94.92
$\Delta E_{n\sigma}^{2*}$				-111.61
$\sum \Delta E^2(3d)$			-14.52	
$\left[\sum \Delta E \right]_{II}$	-59.41	-59.10	-79.57	-175.50
$\left[\sum \Delta E \right]$	-57.30	-63.03	-86.74	-205.12

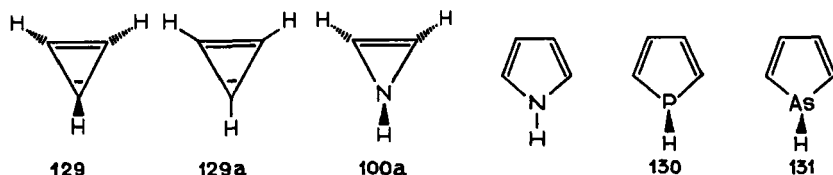
^a The symbol *n* denotes the *p*-type lone-pair orbital in the case of furan, pyrrole, and thiophene and the π -orbital in the case of benzene; the symbols π and π^* denote the usual π and π^* orbitals of ethylene.

and thiophene, on the other, is dictated by the magnitude of the destabilizing interaction $\Delta E_{n\Phi_1}^4$ (Table XIII). The value of this interaction is controlled by the overlap integral, which is decreased in thiophene due to the lengthening of the C—X bond compared to that of pyrrole and furan. The magnitude of $\Delta E_{n\Phi_3}^2$ is also diminished (in absolute value) on going to thiophene. However, this less than that of $\Delta E_{n\Phi_1}^4$, so that ultimately the stabilization of thiophene turns out greater compared to that of pyrrole or furan. Correct trends that characterize the relation between the aromaticities of (48) and (42), and (49) can be revealed only when the *d* orbitals are taken into account. Third, the comparison of the data listed in Table XIII for the heterocycles and benzene shows that the greater aromaticity of benzene stems from the stabilizing interaction between the Φ_2 orbital of the butadiene fragment and the π^* orbital of the ethylene fragment. This interaction, which is absent in the heterocycles, is a strongly stabilizing factor because the energy gap between the Φ_3 and π^* orbitals is small.

The aromaticity of pyrrole, furan, and thiophene may also be assessed by considering the π -electron distribution in them (81JST163), which points to a greater aromaticity of pyrrole and thiophene relative to furan.

Electron distributions are ascertained by means of a Mulliken population analysis of the π -electron atomic populations (in the case of complete π -delocalization, each atom in the 6π -electron five-membered ring would have 1.20 π -electrons associated with it) by determining the spatial extent of the localized orbitals of both the out-of-plane lone pair of the heteroatom and the C=C double bonds as well as through comparing the total electron density plots in planes parallel to the molecular plane.

b. *Aromaticity and the Trend toward Pyramidalization of the Heteroatom.* As was pointed out, to link the antiaromatic character of a molecule with a greater stability of its nonplanar structure compared to the planar one is not fully justified. According to *ab initio* calculations, the cyclopropenide anion $(\text{CH})_3^-$ has nonplanar structure (**129**) with pyramidalized carbon atoms whose preference over the 4π -electron planar structure (**129a**) is the result of the antiaromaticity of the latter. Thus, one may expect that 2-azirine (**100**), which is isoelectronic with $(\text{CH})_3^-$, will have a nonplanar structure (**94a**) with pyramidalized nitrogen atoms. Indeed, semiempirical (73CC688) and nonempirical [83JA(105)396; 87MI3; 89MI5] calculations support this assumption; note that the barrier for nitrogen inversion turns out to be greater [37.7 kcal/mol, MP3/6-31G + p//6-31G + p (89MI5)] than that in NH_3 [5.8 kcal/mol, experiment (62JCP1914)].

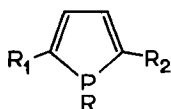
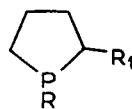


The planar bond configuration of the nitrogen atom in pyrrole is usually explained in terms of aromaticity. The pyramidalization of the phosphorus and arsenic atoms in phosphole (**130**) and arsole (**131**) was taken to be the consequence of their much lower aromaticity relative to pyrrole [75JCS(P2)974] (see Table VIII).

The question of the correctness of such an explanation of the nonplanarity of 2-azirine and the planarity of pyrrole was analyzed in Mo *et al.* [89JMS(201)17]. The evolution of the MOs as a function of the pyramidalization angle in nitrogen was traced. For both 2-azirine and pyrrole nitrogen pyramidalization leads to the stabilization of all π -MOs of the planar structure and, conversely, to the destabilization of several σ -type MOs. In the case of pyrrole, the stabilization of π -orbitals proves insufficient to counterbalance the concomitant destabilization of σ -orbitals. For 2-azirine

the situation is reversed. Consequently, the planar structure of pyrrole and nonplanar structure of 2-azirine are primarily dictated by the σ -frame [89JMS(201)17]. As for the nonplanar geometries of phosphole and arsole, they also are determined not so much by the lower π -aromaticity as by the σ -system (76JA407, 76JA4365). The problems of σ - π separability and the influence of both contributions on the structure of aromatic and antiaromatic six- and five-membered heterocycles have been recently scrutinized (90JA6722). Note, however, that the stabilization of the π -MOs [89JMS(201)17] may, in the case of nonplanar distortions of geometry, be accompanied by a reduction in aromaticity. This occurs, e.g., in the case of benzene distortion (89ZOR673).

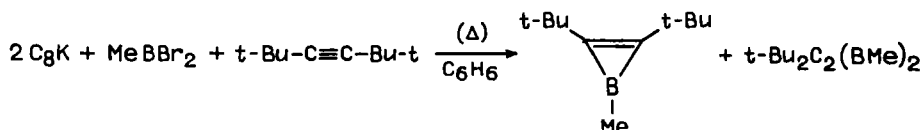
Aromatic cyclic π -electron delocalization does indeed stabilize the planar structure with bond equalization (84ZOR897)—the problem is that, in addition to that effect, there may exist some others that may eventually overshadow it. Thus, the foregoing warrants the conclusion that the preference of a planar or nonplanar geometry of heterocycle depends on a number of factors including aromaticity (antiaromaticity), which may not even be the most important. In any case, this factor should not be disregarded if one wishes to obtain a correct overall energy balance. For example, aromaticity is reflected in the values of inversion barriers. Thus, for antiaromatic 2-azirine the nitrogen inversion barrier is, as was mentioned earlier, 37.7 kcal/mol, whereas in the case of its saturated

**132****133****133a**

analog, aziridine (**132**), this barrier, calculated at the same level, equals 14.9 kcal/mol (89MI5; also see 89MI4). By contrast, in aromatic phosphole (76JA4365) the phosphorus inversion barrier is, according to data on P-substituted phospholes (**133**) (71JA6205), about 15.5 kcal/mol (the value of such a low barrier does not depend essentially on the type of substituent). In the saturated analog (**133a**), it is ~ 36 kcal/mol.

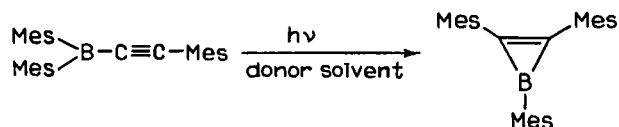
c. *Three-Membered Heterocycles Containing One Heteroatom.* As is evident from the data in Table XII, borirene (**99**) should be regarded as aromatic, and 2-azirine (**100**), oxirene (**123**), and thiirene (**127**) as antiaromatic. The aromaticity of borirene was predicted in the early 1960s by Volpin (62T107), but it was only 20 years later that after numerous unsuc-

cessful attempts (see 84AG444, 84MI2, and the literature cited therein) some borirene derivatives were obtained (84MI2).

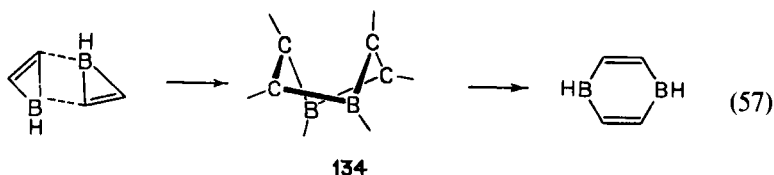


(C₈K is intercalated potassium-graphite.)

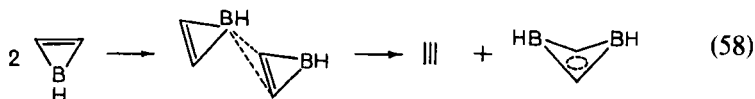
The UV-irradiation of dimesityl(mesitylethynyl)borane in donor solvents induces isomerization to the crystalline trimesitylborirene (87-JA2526). Bulky substituents prevent subsequent dimerization into derivatives of 1,4-diboracyclohexa-2,5-diene, which was the chief obstacle to obtaining borirene. According to *ab initio* calculations (86JA3960), the



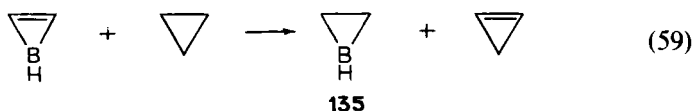
dimerization reaction has a very low activation energy (11.1 kcal/mol) and develops via a highly nonplanar transition state. In structure (134) two boron and two carbon atoms are located in close proximity; the bulky substituents prevent dimerization (57).



The disproportionation of borirene to acetylene and diboretene (58) is slightly endothermic (by ~ 5 kcal/mol), whereas the activation barrier of this BH transfer reaction equals 14.6 kcal/mol (86JA3960). The estimation of the aromatic stabilization energy for isodesmic reaction (59) yields values of 47.5 (6-31G**/6-31G*) (86JA3960), 47.1 kcal/mol (6-31G**/STO-3G), [81JA(103)2589] which makes about 70% of the stabilization energy



of the cyclopropenyl cation The length of the C—B bond in borirene (1.465 Å) (86JA3960) is intermediate between the length of the single C—B bond in CH₃BH₂ (1.574 Å) and that of the double C=B bond in H₂C=BH (1.377 Å) (87MI4) (calculated in all cases with the 6-31G* basis set). According



to X-ray structure analysis of trimesitylborirene (87JA2526) and 2-(2,6-dimethylphenyl)-1,3-dimesitylborirene (90JA1847), the C—B bonds in the borirenes are shortened by an average of 0.10 Å relative to the C—B length in trivinylborane (1.558 Å) and the C=C bond in borirene is elongated by 0.08 Å compared to the same bond in cyclopropene. These features of the geometry of the borirene ring may be regarded, in accordance with the structural criteria, as evidence for the aromaticity of borirene.

The saturated analog of borirene, borirane (**135**), is less stable by 17.5 kcal/mol (6-31G**/3-21G) (85MI4), 13.7 kcal/mol (MP4/6-31G**//3-21G) (86JOM1), than vinylborane. Borirene is, according to *ab initio* calculations (85MI4), more stable than ethynylborane and other open-chain isomers (**136**)–(**139**) [in parentheses, 6-31G**//4-31G-calculated energies are given (in kcal/mol) relative to borirene].

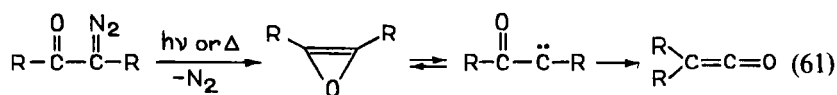
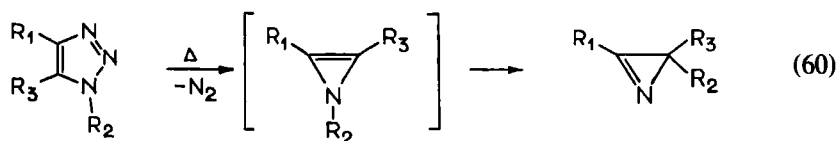


Electropositive substituents stabilize the three-membered ring of borirene, whereas π-donors (NH₂, OH) coplanar with the ring lead to destabilization (85MI4).

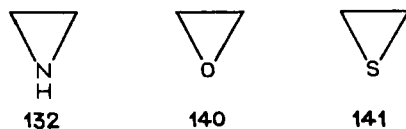
The aromaticity of borirene is obscured by the fact that, owing to its electron deficiency, it is susceptible to nucleophilic attack and, compared to its hydrocarbon analog, is more reactive (84MI2; 90JA1847). The role of aromatic stabilization of borirene may be highlighted by the following example. When the aromatic system is disrupted as a result of a coordination of borirene with O₂, ROH, or R₃N that releases the boron *p*-orbital from π-conjugation, ring cleavage occurs quite easily (90JA1847).

Unlike aromatic borirene, only thiirene of the antiaromatic three-membered ring species (**100**), (**123**), and (**127**) (see Table XII) could be experimentally detected by means of matrix isolation at low temperature [81JA(103)486]. The IR spectrum of thiirene is consistent with the data of *ab initio* calculation [80JA2507; also see 83JA(105)396].

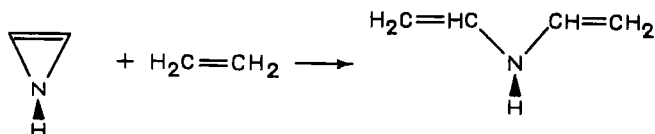
Formation of 2-azirine and oxirene derivatives as intermediates is assumed in a number of reactions, such as (60) and (61). As for the saturated



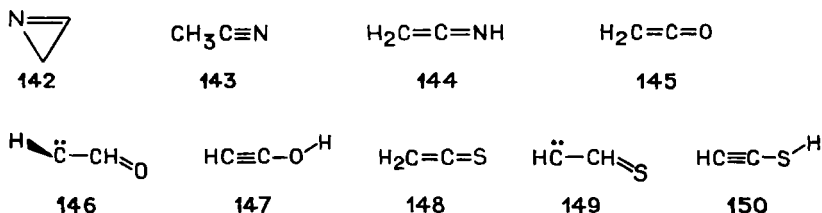
analogs of (100), (123), and (127), i.e., aziridine (132), oxirane (140), and thiirane (141), they are much more stable and have been studied experimentally fairly well (84MI7, 84MI8, 84MI9). Their stability, in contrast to structures (100), (123), and (127), is accounted for not only by the absence of antiaromaticity, but also because their strain energy is somewhat lower. For example, according to estimations from bond valencies, the strain energy of (140) is 26.6 kcal/mol, whereas for (123) it is 31.0, for (132) 29.2,



and for (100) 39.0 kcal/mol [89JMS(187)169]. The 6-31G* calculated HSE of 2-azirine is -80.1 kcal/mol [89JMS(201)17]. 1-Azirine (142), in which



there is no 4π -electron cyclic delocalization, is more stable than 2-azirine (Table XIV). The length of the CN bond in (100) is 1.490 Å, whereas in aziridine (132) it equals 1.449 Å (6-31G* in both cases). For aromatic borirene and borirane, the C—B bond length is smaller in the former case (1.465 and 1.545 Å, 6-31G*) [81JA(103)2589]. As opposed to borirene, the structures (100), (123), and (127) possess higher energies than their open-chain isomers (143)–(150) (73CC688; 78CPL211, 78JCP4244; 80JA7655, 80PAC1623) (Table XIV). Moreover, they have lower kinetic stability; for example, the activation barrier of the rearrangement of oxirene into



formylmethylene (**146**) is as low as 1.2 kcal/mol (CI-SD, 4-31G) (80JA7655).

The 6-31G** calculations have shown [89JMS(187)169] that with rising temperature the equilibrium constant of the isomerization 2-azirine-1-azirine is lowered substantially [see Eq.(60)], which should result in an increased concentration of the less stable 2-azirine. The difference between the energies of the aza-substituted derivatives of 2- and 1-azirines, namely, isodiazirine (**151**) and diazirine (**152**), is slightly less [34.3 kcal./mol, 3-21G (83MI3)] than that in (**100**) and (**142**). Whereas 2-azirine is destabilized relative to 1-azirine and open-chain isomers, 2 π -electronic cyclic structure (**153**), isoelectronic with borirene (**99**), is according to MP4 SDQ/6-31G**//DZ + P calculations [89JCS(F2)187], the most stable C_2NH_2^+ isomer. The length of the CN bond in (**153**) is, in contrast to 2-

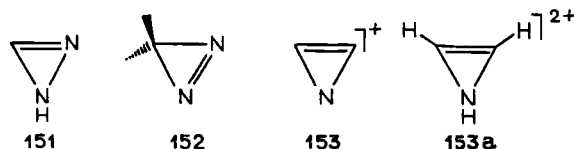
TABLE XIV
AB INITIO-CALCULATED ENERGIES (IN kcal/mol)
OF C_2XH_2 (X = NH, O, S) ISOMERS RELATIVE
TO THE ENERGIES OF 2-AZIRINE, OXIRENE,
AND THIRIRENE

C_2NH_3 [6-31G (79NJC365)]			
Structure	142	143	144
E_{rel}	-33 ^a	-100	-69
C_2OH_2 (DZP, CI-SD (Q) (80JA7655))			
Structure	145	146	147
E_{rel}	-80.6	-0.9	-44.0
C_2SH_2 [STO-4G (78CPL211)]			
Structure	148	149	150
E_{rel}	-29.3	-15.3	-30.2

^a According to MP2/6-31G //6-31G** calculations [89JST(187)169] 2-azirine is less stable than 1-azirine by 42.7 kcal/mol.

^b MCSCF/6-31G* calculations [87JCS(F2)1629] indicate that oxirene is more stable by 4.2 kcal/mol than formylmethylene.

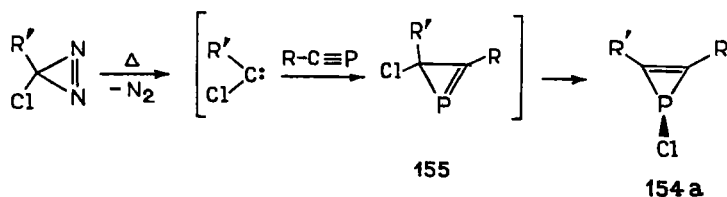
azirine, quite small (1.314 Å). Thus, the aromatic structure (**153**) and antiaromatic structure (**100**) differ in principle regarding their stability relative to isomers.



Ab initio calculations have shown (89JA6976) that the cyclic 2π -electron 2-azirine dication $\text{C}_2\text{H}_2\text{NH}^{2+}$ (**153a**) has an energy higher by only 8.4 kcal/mol (MP4/6-311 G**//MP2/6-31G* with ZPVE correction) than that of the open-chain isomer of $\text{CH}_2\text{NCH}^{2+}$. The reverse order regarding the energies of the cyclic and the open-chain isomers of $\text{C}_2\text{H}_3\text{N}^{2+}$ compared to the corresponding isoelectronic isomer of C_3H_3^+ is explained as follows. The aromatic stabilization of (**153a**) proves insufficient to offset the Coulomb repulsion between the positively charged hydrogen atoms, which is greater in cyclic than in open-chain structures (89JA6976). Calculations indicate that the cyclic structure (**153a**) corresponds to a minimum on the $\text{C}_2\text{H}_3\text{N}^{2+}$ PES and is potentially observable. 2-Phosphirene (**154**)



is, apparently, less antiaromatic than 2-azirine. Thus, for example, the reaction of chloro-substituted diazirines with kinetically stabilized phosphalkynes leads not to 1-phosphirene (**155**) but rather to its isomer, 2-phosphirene (**154a**), via a chlorine shift (89JA6976; 90CRV191), cf. Eq. (60).



d. *Five-Membered Heterocycles.* Judging from the data listed in Table XII, the 4π -electron structure of borole (**98**) belongs to an antiaromatic species, yet the Hückel rule cannot be applied to borole unconditionally since in this molecule the HMO-calculated antibonding and nonbonding π -MOs are vacant.

Unsubstituted borole (**98**) has not been obtained, but its derivatives are known, e.g., pentaphenylborole (86JA379). Its high reactivity as well as the ^1H -NMR and electronic spectra have been interpreted in terms of antiaromaticity (86JA379).

According to MNDO calculations (our unpublished results), the ground state of borole is, as distinct from the isoelectronic cyclopentadienyl cation, a singlet. The planar structure of the triplet 3B_2 state corresponds to a minimum on the PES. However, its energy is higher than that of the 1A_1 state structure (Table XV). Bond length alternation in the former is less pronounced than in the structure of the ground state (**77**). Calculations of index A (our data) and RCI (86T4177) show that the lowest excited triplet 3B_2 and singlet 1B_2 states of borole are moderately aromatic (RCI for 3B_2 and 1B_2 is 1.48, whereas in the case of 1A_1 state it is 1.14).

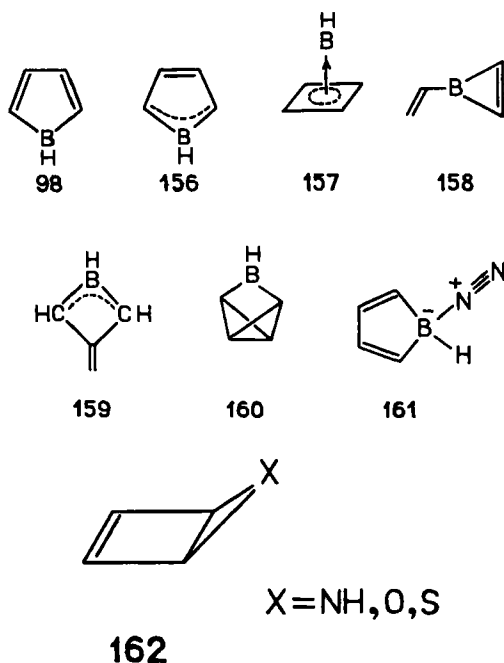
Structure (**156**) of the singlet state with pyrrole-type geometry [$2b_1$ HOMO rather than the a_2 MO as in (**98**)] has, as expected from the relationship between electronegativities (85MI6), a higher energy (Table XV). The pyramidal structure (**157**), which meets the requirements of three-dimensional aromaticity (87MI2), has a higher energy than borole (82JA4781).

Among the isomers of C_4BH_5 (**157**)–(**160**), borole is the most stable (Table XV), which may be attributed to its smaller antiaromaticity relative to the cyclopentadienyl cation. Similar to borabenzene, borole is apt to act as a strong Lewis acid complexing even with nitrogen; thus structure (**161**) corresponds to a minimum on the PES; $R(\text{BN}) = 1.561 \text{ \AA}$ (our MNDO data). Like benzene, 6π -electron pyrrole, furan, and thiophene are stable compared to other cyclic valence isomers, e.g., Dewar's structures (**162**). Dewar furan and Dewar thiophene (**162**, $\text{X} = \text{O}, \text{S}$) have been obtained only under conditions of low-temperature photolysis along with

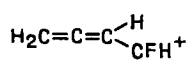
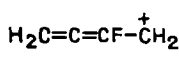
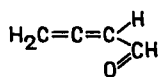
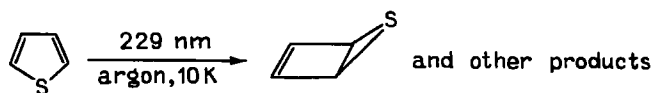
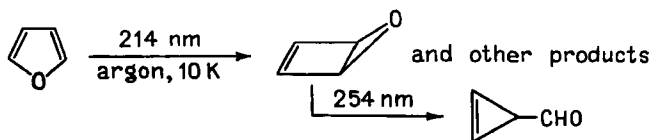
TABLE XV
RELATIVE ENERGIES (IN kcal/mol) OF BOROLE ISOMERS CALCULATED BY THE
MNDO METHOD^a

Structure	98 (1A_1)	98 (3B_2)	156	157	158	159	160
Relative energy	0	13.6	33.9	65.4	13.2	35.4	59.0

^a Unpublished results.

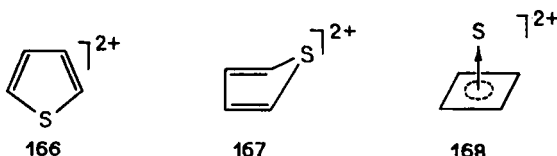


other products; owing to secondary photolysis, they may undergo re-arrangements (86JA1691).



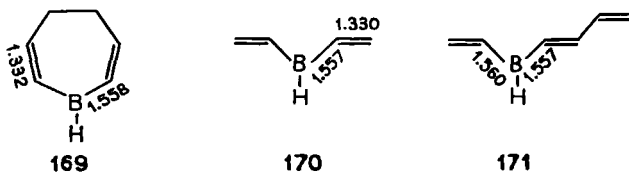
According to *ab initio* calculations with a (4s2p/2s) basis set [86JCS(P2)1857], the open-chain isomer (**163**) of furan has an energy higher by 23.7 kcal/mol than that of (**49**). As the electronegativity of the hetero-atom is increased, the aromatic character is gradually lost and, e.g.,

the 6π -electron structure (**29a**) of the fluorophenium ion has an energy 6.2 kcal/mol higher than that of the open-chain isomer (**164**) and is more stable than the open-chain structure (**165**) by a mere 4.0 kcal/mol [86JCS(P2)1857]. However, the C_{2v} planar structure (**166**) of the 4π -electronic dication of thiophene does not correspond to a minimum on the PES (MINDO/3) (82ZOR2009) and is distorted into a C_s structure (**167**) whose energy is 32 kcal/mol higher than that of the pyramidal structure (**168**).

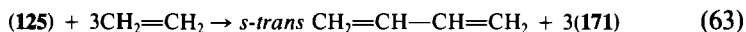
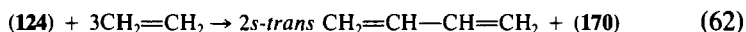


e. *Seven-Membered Heterocycles.* The 8π -electron planar structures of 1*H*-azepine, oxepine, and thiopine (**125**, **126**, **128**) may be classified as antiaromatic and 6π -electron borepin (**124**) as aromatic. At the same time, the data of Table XII indicate that the aromaticity or antiaromaticity of these compounds is a good deal lower than those of the preceding members of the series.

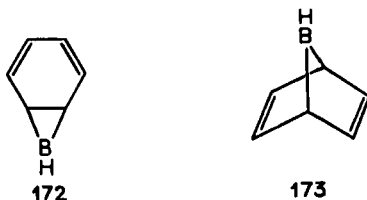
As judged from the TRE values (Table XII), borepin (**124**) possesses less aromaticity than borirene (**99**). The 6-31G* calculations (89MI6) show that it has a planar structure with the B—C bond being shorter than in the case of dihydroborepin (**169**) (1.537 and 1.558 Å). Comparison of the B—C, C=C (1.349 Å), and C—C (1.351 Å) bond lengths in borepin with the lengths of the same bonds in the reference compounds (**169**)–(**171**) shows that in the former the C=C double bond grows longer whereas the C—C single bond is reduced, which may be taken as a result of cyclic π -electron conjugation (89MI6).



The determination of the energy of aromatic stabilization of borepin by calculating the energies of isodesmic reactions (62) and (63) with a correction for the strain leads to the value 12.7 kcal/mol (89MI6). The same energy calculated with the same basis set (6-31G*) is for benzene 24.7 kcal/mol and for borabenzene 19.2 kcal/mol.

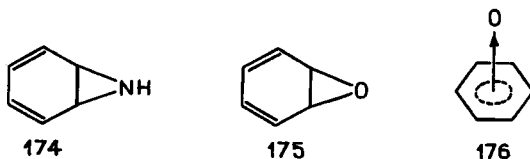


According to a calculation of the structural index *A* (MINDO/3 geometry) [81JOM(215)315], the aromatic character of the recently synthesized 1-methylborepin (87CL1451) amounts to 75% of that of benzene. The greater stability of borepin's planar structure relative to those of its valence isomers (172) and (173) is thought to be a manifestation of its aromaticity: $\Delta E [(172) - (124)] = 37.7$ and $\Delta E [(152) - (103)] = 23.6$ kcal/mol (6-31G*//STO-3G) (83TL1863).



The MP2/4-31G/STO-3G calculations show (83TL1863) the tropylium cation to be 112.7 kcal/mol more stable than the hypothetical bicyclo [4.1.0]hepta-2,4-dien-7-yl cation. This difference, attributed to the effects of aromatic stabilization, should be compared with the value of $\Delta E (172) - (124) = 44.8$ kcal/mol (at the same computational level). Therefore, the energy of aromatic stabilization of borepin comes to about 40% of that of the tropylium cation. The 6-31G*/6-31G* calculated $\Delta E (172) - (124) = 37.6$ kcal/mol, whereas nonaromatic cycloheptatriene is a mere 5.2 kcal/mol (same computational level) more stable than norcaradiene (6.2 kcal/mol by experimental estimate) (84JA7696).

The structures of 1H-azepine (125) and oxepine (126) assigned to the antiaromatic class actually turn out to possess a higher energy than their valence isomers (174) and (175): $\Delta E[(175) - (125)] = 7.2$ kcal/mol (STO-3G) [84JMS(110)277]; $\Delta E[(175) - (126)] = 1.7$ kcal/mol (exper.) (87CL1451), 1.1 kcal/mol (MP2/6-31G*) (84JA7696), 0.8 kcal/mol (MP3/6-31G*) (89CRV1225). According to X-ray data on substituted azepines and oxepines (81AG713; 86CC970), these molecules have nonplanar boat-like structures. The results of low-temperature ^{13}C -NMR studies on 2-



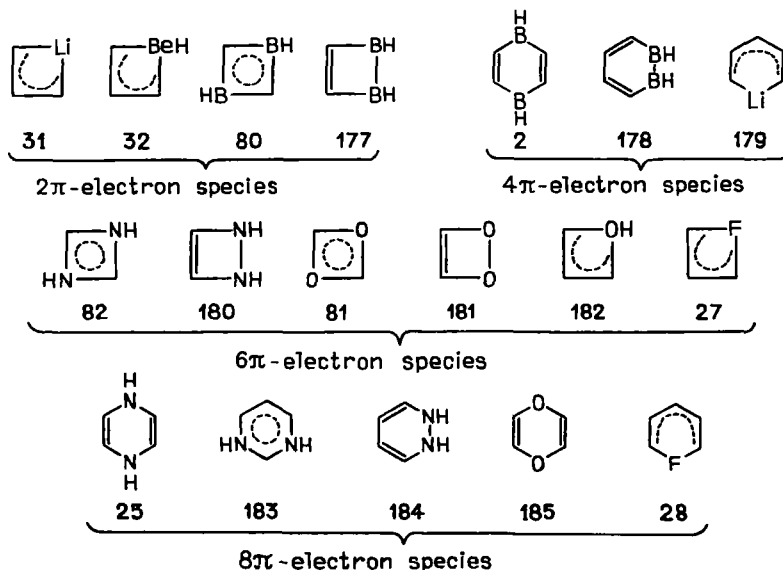
cyano-7-ethyloxepine bear witness to its nonplanar ring geometry with the ring inversion barrier at 135K $\Delta G^\ddagger = 6.50 \pm 0.2$ kcal/mol (86CC970).

The STO-3G (84M11) and 3-21G (84JA7696) calculations have shown that the bond lengths in planar structures of azepine and oxepine are nearly the same as those in the nonplanar ones, and close to the bond lengths typical of planar acyclic polyene. The difference between the energies of the planar and nonplanar structures of azepine and oxepine is insignificant (3 and 2 kcal/mol). It is even smaller than in the case of cycloheptatriene (6 kcal/mol) [84JMS(110)277], which is devoid of any antiaromatic destabilization. Thus, no unmistakable manifestations of antiaromaticity have been detected in azepine and oxepine. The pyramidal structure (176) of oxepine valence isomer has a higher energy than (126) (by 148.4 kcal/mol, MINDO/3); it does not correspond to a minimum on the PES (84ZOR897).

We shall not go with our analysis beyond the seven-membered rings. For larger ring analogs of the pyrrole type, the interested reader may find relevant material in reviews (75PAC691; 78AHC55).

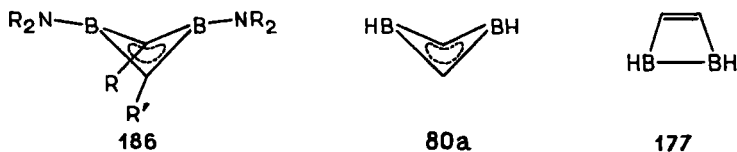
B. HETEROCYCLIC COMPOUNDS ISOELECTRONIC WITH THE DOUBLE-CHARGED PARENT ANNULENE ION

This section is devoted to heterocyclic molecules isoelectronic with dications and dianions of the molecules that are central to the aromaticity concept, i.e., cyclobutadiene and benzene (Scheme 5). 1,3-Diboretene

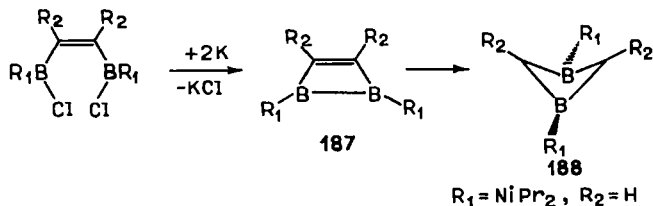


SCHEME 5

(**80**) is isoelectronic with the dication of cyclobutadiene, which has a D_{2d} structure. According to X-ray data on 1,3-bis(dimethylamino)-2,4-di-*tert*-butyl-1,3-diboretene (**186**) [84AG(E)371] as well as *ab initio* calculations [81JA(103)2589, 81MI1; 84AG(E)374; 85JA2773], 1,3-diboretene has a nonplanar C_{2v} structure (**80a**). The inversion barrier through the planar



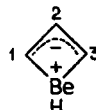
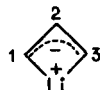
D_{2h} structure equals 18.6 kcal/mol (MP3/6-31G*) (85JA2773). Comparison with the inversion barrier of the cyclobutadiene dication (7.5 kcal/mol) indicates a lower aromatic stabilization energy for the planar structure of 1,3-diboretene (85JA2773). The length of the B—C bond in the latter (1.504 Å, X-ray) [84AG(E)371] (1.500 Å, 6-31G*) (85JA2773) is close to that in borirene (1.465 Å) (90JA1847). 1,2-Diboretene (**177**) is less stable by 16.9 kcal/mol than 1,3-diboretene (MP3/6-31G*//6-31G*) (85JA2773). The activation energy of the (**177**) \rightarrow (**80a**) isomerization is 8.3 kcal/mol (the same computational level) (85JA2773). A recently synthesized derivative of 1,2-diboretene (**187**) isomerizes into (**188**) upon heating in toluene to 120°C [85AG(E)759]. X-ray analysis of (**187**) [85AG(E)759] and *ab initio* calculations (85JA2773; 87JA6290) show that, unlike 1,3-diboretene, in 1,2-diboretene the C_2B_2 ring is planar. The bond lengths



[BB 1.75 Å (X-ray), 1.715 Å (6-31G*) (85JA2773), BC 1.58 Å (X-ray), 1.559 Å (6-31G*); CC 1.31 Å (X-ray), 1.364 Å (6-31G*)] indicate a structure with double-bond fixation [81JA(103)2589; 85AG(E)759]. According to the values of the RCI (**177**) = 1.219 and RCI (**80a**) = 1.548 (84JOC4475), 1,2-diboretene is to be classified as nonaromatic, and 1,3-diboretene as aromatic. 1,3-Diboretene is also more stable than its other valence isomer, diboratetrahedrane (**189**), which has a triplet electronic state (ΔE (**189**) – (**80a**) = 67.8 kcal/mol (MP3/6-31G*//3-21G) (85JA2773).



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Ab initio (86MI6) and MNDO [81JOM(219)279] calculations show that lithiacyclobutadiene (**31**) and its beryllium analog (**32**) have planar 2π -electron C_{2v} structures. According to Mulliken population analysis, lithium participates in the π -system only to a slight degree, and structure (**31**) is characterized by a sizeable separation of charges which are -0.27 (C1), -0.46 (C2), and $+0.47$ (Li) (3-21G) (86MI6). There is considerable charge separation also in (**32**) (-0.32 at C2 and $+0.57$ at Be) (86MI6). Both structures possess fairly large stabilization energies, which can be found from the isodesmic reaction (64)

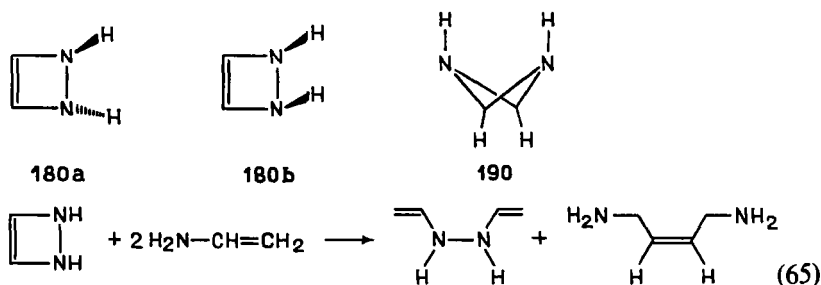


$\Delta E(X = Li) = -51.5$ kcal/mol and $\Delta E(X = BeH) = -38.1$ kcal/mol (3-21G) (86MI6).

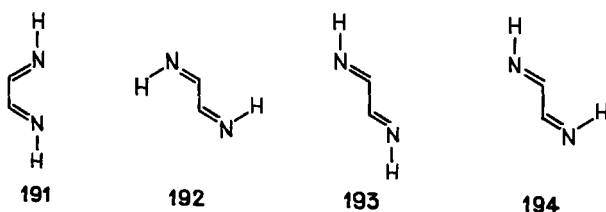
Similar to 2π -electronic structures (**80**) and (**177**), the 6π -electronic planar structures (**82**), (**180**), (**181**), and (**81**) satisfy the Hückel rule. These are isoelectronic with the cyclobutadiene dianion, which does not possess aromatic stabilization (Table I). According to the values of the RCI [1.396 (**82**) and 1.059 (**180**) (84JOC4475)], 1,3-diazetene (**82**) and 1,2-diazetene (**180**) should be assigned to the class of nonaromatic compounds. As already noted, the planar 6π -electron D_{2h} structure (**82**) does not even correspond to a minimum on the PES (80ZOR681; 87JA6290; 90JA4155). In the structure of 1,2-diazetene (**180**) both nitrogen atoms are pyramidalized; the anti-conformation (**180a**) is 4.1 kcal/mol more stable than the syn one (**180b**) (MP2/6-31G*) [89JMS(201)17]. The energy of the completely planar C_{2v} structure of 1,2-diazetene is 21 kcal/mol higher than the syn conformation (**180b**) (87JA6290). Both structures (**180a**) and (**180b**) as well as structures (**190**) are considerably destabilized relative to open-chain isomers (**191**)–(**194**) (Table XVI). Calculation of the HSE using reaction (65)

TABLE XVI
AB INITIO-CALCULATED RELATIVE ENERGIES (IN kcal/mol) OF $(CHNH)_2$ ISOMERS

Structure:	82	180a	180b	190	191	192	193	194
$E_{rel.}$								
MP2/6-31G* //3-21G (87JA6290)	56.1	43.6	49.3	54.4	—	2.8	0	2.0
MP2/6-31G* //6-31G* (62JCP1914)	—	45.7	49.8	—	7.6	2.8	0	2.6



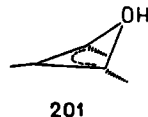
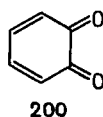
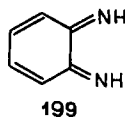
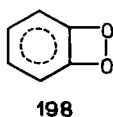
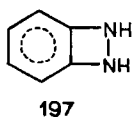
yields a value of -44.2 kcal/mol (6-31G*) [89JMS(201)17], which clearly indicates the absence of any aromatic stabilization (even when corrections for nitrogen lone-pair repulsion and strain energy are taken into account).



In the planar D_{2h} structure of 1,3-dioxetene (**81**), the length of the C—O bond (1.325 Å; 6-31G**) (90JA4155) is close to that of the single C—O bond in vinyl alcohol (1.35 Å; 6-31G*). In structure (**181**) the C—O length is 1.38 Å (87JA6290). High energies of 1,3- and 1,2-dioxetenes relative to the open-chain isomer, glyoxal (**195**), equally point to the absence of aromatic stabilization [ΔE (**81**) – (**195**) = 75.4 kcal/mol, ΔE (**181**) – (**195**) = 87.9 kcal/mol; MP2/6-31G* (87JA6290)]. The D_{2h} structure does not even correspond to a minimum on the PES. The nonplanar dioxacyclobutane structure (**196**) has an energy lower by 8.4 kcal/mol (MP2/6-31G*)



than that of 1,2-dioxetene (87JA6290). The instability of structures (**82**) and (**81**) compared to the open-chain isomers is manifested in the instability of their benzoderivatives (**197**), (**198**) relative to the quinonoid forms (**199**) and (**200**). As has been shown by nonempirical calculations with the 3-21G basis set (88ACS428), *o*-benzoquinone (**200**) and its diimine (**199**) are more stable than bicyclic structures (**197**) and (**198**) by, respectively, 65.9 and



23.2 kcal/mol. The calculated CN and CO bond lengths in (197) and (198)—1.460 and 1.434 Å, respectively—are close to those of the single C—N and C—O bonds in CH₃NH₂ (1.471) and CH₃OH (1.441 Å).

In the planar 6 π -electron structures of oxacyclobutadiene (182) and fluoracyclobutadiene (27), the AM1-calculated C—O (1.500 Å) and C—F (1.469, 1.479 Å; STO-3G) bond lengths are greater than those in CH₃OH (1.410 Å) and CH₂CHF (1.374 Å) (our unpublished data). Unlike structure (27), planar structure (182) does not correspond to a minimum on the PES; it is distorted with no barrier to the nonplanar C_s structure (201), whose energy is 22.2 kcal/mol lower.

Structures (23) and (178) are isoelectronic with benzene dication. A number of substituted (23) structures are known which can be formed, for example, through dimerization of borirene (84MI2). The 3-21G-calculated C=C bond length in 1,4-diboracyclohexadiene (23) (1.338 Å) (90JA1847) is slightly greater than that of the same bond in ethylene (1.315 Å; 3-21G). In structure (178) both boron atoms are pyramidalized, which may be regarded as a manifestation of a trend toward interruption of antiaromatic cyclic conjugation (86JA3960). The planar structure (178) has a somewhat higher energy (Table XVII). Structures (23) and (178) are less stable than the pyramidal structure (202), which satisfies the electron-count rule for pyramidal structures (86JA3960)

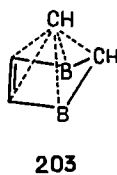
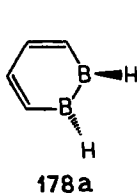
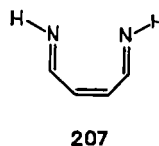
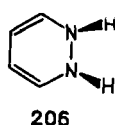
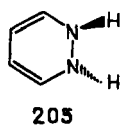


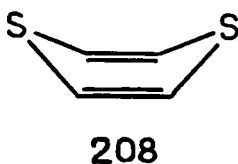
TABLE XVII
RELATIVE ENERGIES (IN kcal/mol) ESTIMATED AS
 ΔE (MP2/6-31G* //3-21G + MP3/6-31G//3-
21G - 6-31G //3-21G) OF SOME VALENCE ISOMERS
OF 1,4-DIBORACYCLOHEXADIENE (23) (90JA1847)

Structure:	23	178	178a	202	203
E_{rel}	23.9	43.8	43.0	0	40.2

Also, the planar 4π -electron structure (**179**) corresponds to a minimum on the PES (unpublished results). Similar to 4π -electron structure (**23**), it is less stable relative to its pyramidal isomer (**204**) ($\Delta E = 50.3$ kcal/mol; MNDO). The 8π -electronic planar structures (**25**), (**183**), (**184**) have higher energies compared to structures where the nitrogen atoms are pyramidalized [82ZSK23; 83AG(E)171, 83JA(105)707; 84JST(109)277; 88JOC2127; 89JMS(201)17]. According to ^1H -NMR spectral data on 1,4-bis(trimethylsilyl)-1,4-dihydropyrazine [81AG(E)599; 83JA(105)707] and ring current calculations on (**25**), (**183**), and (**184**) (86MI10), these compounds are paratropic antiaromatic systems. For 1,2-dihydropyridazine, as in the case of 1,2-diazetidine, anti-conformation (**205**) is preferred (by 10.5 kcal/mol; 6-31G* //6-31G* [89JMS(201)17] over syn conformation (**206**). However, unlike 1,2-diazetidine, the open-chain form (**206**) is not stabilized to any great extent ($\Delta E[(\text{205}) - (\text{207})] = 0.4$ kcal/mol; 6-31G*//6-31G*) [89JMS(201)17], thus emphasizing the role of ring strain in the destabilization of 1,2-diazetidine structure (**180**). The energy of planar structure (**184**) is higher by 13.1 kcal/mol than that of (**205**) [89JMS(201)17].



1,4-Dioxin (**185**) has a DRE value equal to -5 kcal/mol [6-21G calculations (88JOC2127) in accordance with the DRE scheme, and a SCF π -MO calculation (71JST236) yields -1.3 kcal/mol]. These values warrant the assignment of this compound to the nonaromatic class. The structural criterion of aromaticity based on the calculated energy change during folding of the planar structure (88JOC2127) points to the same conclusion. According to its far-infrared spectrum (73JCP4344) and electron diffraction data (84MI11), 1,4-dioxin has a planar structure and, as has been shown by *ab initio* calculations (88JOC2127), folding of the ring increases the energy. The analog of (**185**), 1,4-dithiin, has, according to experimental (54AX498; 82AJC2335) and calculational [81JST159; 84JMS(108)59] data, a nonplanar structure (**208**). However, the difference between the energies



of the planar and boat structure is insignificant (2.3 kcal/mol; 3-21G*) [84JMS(108)59] and, following Podlogar *et al.* (88JOC2127), 1,4-dithiin is to be classified as nonaromatic.

As distinct from 1,4-dioxin (185), the isoelectronic 8π -electron cation (209) shows a closer resemblance to the antiaromatic benzene dianion; for example, there is a first-order Jahn–Teller effect in the lowest singlet state of D_{3h} structure of (209) ($^1E'$ state) and the C_{2v} structures (210) and (211) possess lower energies relative to it. The cation (209) has a triplet $^3A_{2g}$ ground state. The nonplanar C_{3v} structure (212) with a closed electronic shell has an energy 62.1 kcal/mol higher than the energy of the $^3A_{2g}$ state (MNDO) (unpublished results).



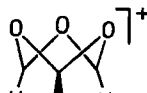
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V. Nitrogen and Phosphorus Analogs of Annulenes and Monocyclic Conjugated Ions

Of particular interest are the completely substituted structures of heterocyclic compounds containing no carbon atoms, such as tetrazete (61) and hexazine (41), which represent inorganic heterocycles. Now the question arises whether it is aromatic stabilization that renders structures (41), (60), (213)–(216) amenable to experimental observation or whether some other factors primarily determine their geometry and stability. Furthermore we shall also examine the electronic structure and stability of the corresponding phosphorus rings. This can reveal certain differences concerning the role of aromatic stabilization effects in the two classes of conjugated cyclic molecules formed, respectively, by the main group elements of the second and the third rows. In greater detail these differences will be dealt with in Section VI.



213



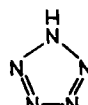
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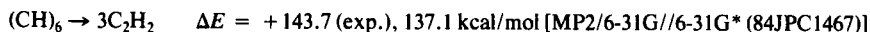
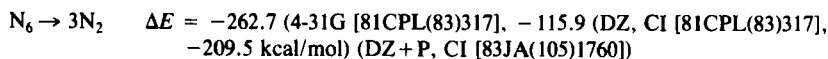


41

A. SPECIFIC FEATURES OF THE ELECTRONIC STRUCTURE OF NITROGEN AND PHOSPHORUS RINGS COMPARED WITH THE CORRESPONDING PARENT HYDROCARBONS

Comparison of the strengths of $\text{HN}=\text{NH}$ and $\text{HP}=\text{PH}$ π -bonds [63.5 and 36 kcal/mol; MC SCF/6-31G**/3-21G* calculations extended by means of the second-order CI calculations (86IC248) found from the values of rotational barriers with an experimental $\text{C}=\text{C}$ π -bond strength (65 kcal/mol) (55JCP315)] shows that the $\text{N}=\text{N}$ π -bond is close in strength to the $\text{C}=\text{C}$ π -bond, whereas the $\text{P}=\text{P}$ π -bonds are about half as strong. [In Schleyer and Kost (88JA2105), in order to evaluate the π -bond energy E_π , the difference in energy between two single bonds and a double bond was calculated by means of isodesmic reactions and then E_π was found by subtracting this difference from the dissociation energy of the single-bond system. With experimental data in this scheme $E_\pi(\text{C}=\text{C}) = 70.6$ kcal/mol (88JA2105).] Thus, one may expect that the effects of cyclic π -electron delocalization will, for example, in hexazine be as strong as in benzene, whereas in hexaphosphobenzene they will be much weaker. Indeed, comparison, in the context of the structural criterion of aromaticity, of the *ab initio*-calculated NN bond length in hexazine (1.288 Å, DZ+P) [83JA(105)1760] [1.284 Å, 4-31 G* (89JPC5722)] with the N—N bond length in hydrazine (1.447 Å) and with the $\text{N}=\text{N}$ bond length in diazene (1.25 Å) as well as the values for hexazine of QMRE (88IC2219) (RCI = 1.792) (83JOC1344) and DRE calculated in π -approximation (88ZOR24) reveals they exceed the bond length for benzene. All this evidence points to greater aromaticity of hexazine relative to benzene.

However, in contrast to benzene (Table IX), hexazine is thermodynamically unstable with respect to decomposition into molecular nitrogen



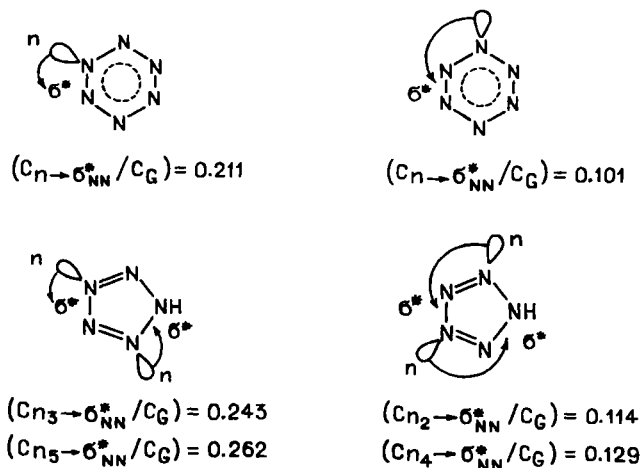
Ab initio calculations show [83JA(105)1760] that the D_{6h} structure of hexazine corresponds to a very shallow minimum on the PES. Hexazine has been detected experimentally by means of the low-temperature matrix isolation (80AG745) but, according to [83JMS(105)351], this result still requires verification.

Since the aromaticity of hexazine and benzene is of about the same degree, evidently, the instability of the former must be related to some specificities of the σ -system. A detailed analysis of the factors that determine the instability of the nitrogen and phosphorus rings based on the

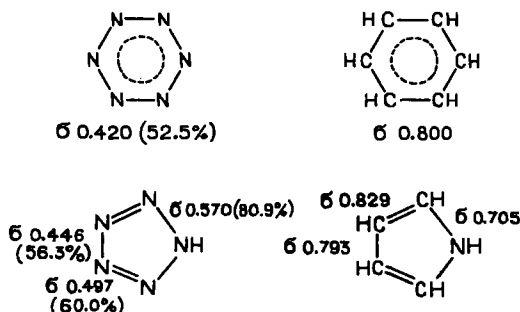
molecule-in-molecule approach is available (87JA3234). In this approach, the wave functions are represented by a linear combination of electron configurations based on the orbitals of the component subsystems:

$$\psi = C_G\phi_G + C_T\phi_T + C_E\phi_E \quad (66)$$

In Eq. (66), the first configuration ϕ_G is termed the ground configuration for which there is no electron shift between any pair of subsystems, nor is there electron promotion in any subsystems. It is the second configuration ϕ_T that is of interest for the problem in hand. It is an electron-transferred configuration (an electron is shifted from the occupied orbital of a subsystem to a vacant orbital of another subsystem); ϕ_E is the locally excited configuration, and C_G , C_T , and C_E are the coefficients of the electron configurations. The values of these coefficients provide information on specific features of the electronic structure of a molecule. Calculated values of the C_T/C_G ratio for hexazine (**41**) and pentazole (**216**) show that the N—N single bonds in them are destabilized by a flow of the lone pairs of electrons. For these compounds, (**41**) and (**223**), the geminal inflow (0.211 and 0.262, respectively) (Scheme 6) exceeds the corresponding values in hydrazines (0.110) and diazene (0.183), whereas the vicinal inflow values are greater (0.101 and 0.129, respectively) than that for tetrazadiene (0.064) (Scheme 6). Comparison between the π and σ components of the atomic bond population in the nitrogen rings of hexazine and pentazole and in those of the parent structures of benzene and pyrazole (Scheme 7) shows (87JA3234) that in the case of the former compounds the values of



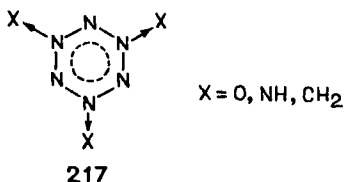
SCHEME 6



SCHEME 7

the π -components amount to $\sim 80\%$ of those for benzene and pyrazole, whereas the values the σ -components make 50–60%, with the exception of the triazene conjugation in pentazole. Thus, the in-plane bonding proves to be much weaker in the nitrogen rings than in the parent hydrocarbon or monoheteroatomic structures.

Since the main condition conducive to destabilization of the NN bonds in the rings (41), (61), (213)–(216) is the presence on either side of each of these bonds of geminal and vicinal sp^2 lone pairs of electrons, the obvious approach to the stabilization of these structures consists of the introduction of substituents that would check the flow of electron lone pairs into σ^* -orbital (87JA3234). This conclusion clearly supports the scheme, proposed in Glukhovtsev *et al.* (88KGS250), for stabilizing the nitrogen and phosphorus rings. As has been shown (88KGS250, 88ZOR2486) by MNDO, the destabilization of, e.g., hexazine, is substantially reduced in the structure of the (217) type



B. THREE-MEMBERED AND FIVE-MEMBERED NITROGEN AND PHOSPHORUS RINGS

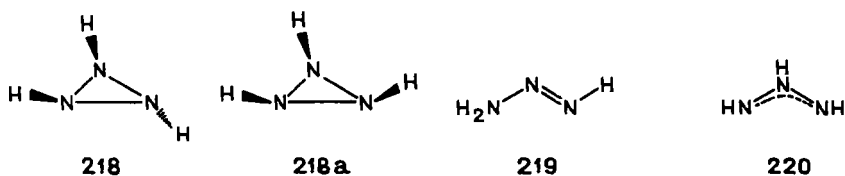
According to *ab initio* calculations (74JA4753; 88MI6), the 2 π -electron D_{3h} structure (213) corresponds to a minimum on the PES; however, it has a much higher energy (by ~ 60 kcal/mol, DZ + P) (88MI6) than the energy

of the linear structure N_3^+ ($^3\Sigma_g^-$ ground state). It will be recalled that an analogous 2π -electron cyclic structure of the cyclopropenyl cation is more stable than its open-chain isomer. The relative stability of the cyclic and open-chain isomers of N_3^+ is, apparently, determined mainly by the σ -system (80PAC1443).

Experimental data on the $^{14}N\ ^{15}N/^{14}N_2$ matrix bombarded with 4 keV $Ne + Ne^+$ (20 K) allow the transient formation of a cyclic structure (**214**) to be assumed (88JA7225). Similar to the isoelectronic cyclopropenide anion, the D_{3h} structure of N_3^- has a triplet $3A'_2$ ground state, $R(NN) = 1.362\text{ \AA}$ (6-311 + G*). The S - T energy gap in (**214**) is 39 kcal/mol, according to CI calculations including up to quadruple excitations in the σ and π spaces (88JA7225).

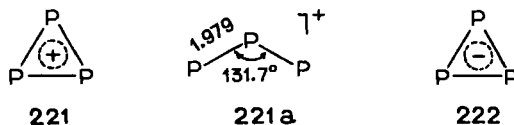
Antiaromatic structure (**214**) has an energy higher by 18.7 kcal/mol relative to the bent acyclic structure (3B_2 state) and by 42.7 kcal/mol compared to the linear structure N_3^- ($^1\Sigma_g^+$ state) (88JA7225).

The 6π -electron planar structure of triaziridine (NH)₃ satisfies the Hückel rule. However, the filling of all the bonding and antibonding π -orbitals leads to a net resonance energy equal to zero. Thus, triaziridine isolated in the form of an Ag^+ -zeolite complex (77JA7057) is to be regarded not as an aromatic but rather as a nonaromatic molecule (80PAC1443). *Ab initio* calculations show (73TCC1; 84HCA1918; 88JA3435) that the nitrogen atoms are pyramidalized in the triaziridine structure. The C_s structure (**218**) is more stable than the C_{3v} *cis* structure (**218a**) [by 13.4 kcal/mol, MBPT (2)/6-31G**/6-31G* (88JA3435)]. The energy of (**218**) is higher by, respectively, 41.4 and 25.8 kcal/mol [CI-SDTQ-MBPT (4)/DZP//MBPT (2)/DZP] than that of triazene (**219**) and triimide (**220**). According to *ab initio* calculations on the triaziridine dication (NH)₃²⁺ whose planar D_{3h} structure is π -isoelectronic with the cyclopropenide anion (80JA5302), also the dication is characterized by pyramidalization of the nitrogen atoms in the structures of both the ground singlet $^1A'$ state and the lowest triplet $^3A''$ state.

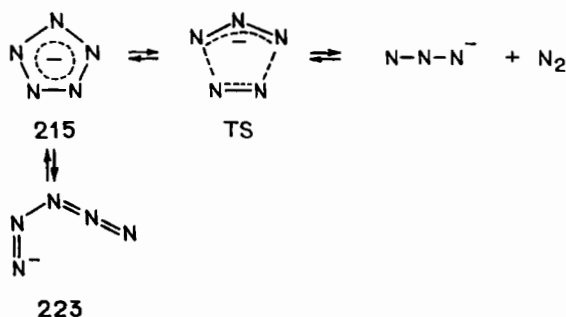


The bond length in the planar 2π -electron D_{3h} structure P_3^+ (**221**) is 1.952 Å, whereas in the $H_2P \cdots PH^+$ ion it is 1.846 Å (MNDO) (84CJC341). The D_{3h} structure of P_3^+ (**221**), $^1A_1'$ state, $R(PP) = 2.077\text{ \AA}$, is more stable by, respectively, 70.8 and 52.3 kcal/mol than the C_{2v} struc-

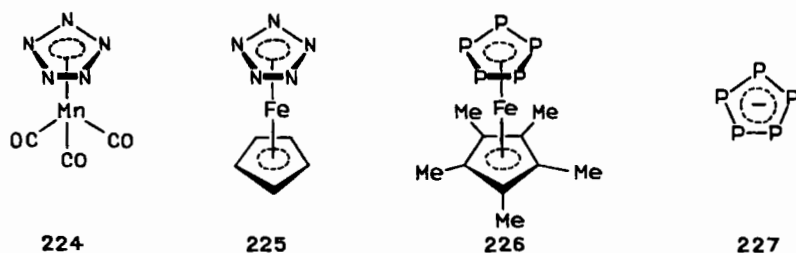
ture (**221a**), 1A_1 state, and the linear $D_{\infty h}$ structure, $^3\Sigma_g^-$ state, $R(PP) = 2.054 \text{ \AA}$ (MP3/DZ + P//DZ + P calculations) (88MI6). The activation barrier of the (**221**) \rightarrow (**221a**) isomerization amounts to 85.1 kcal/mol (the same level of calculation) (88MI6). These differences in the relative stability of the cyclic vs open-chain isomers N_3^+ and P_3^+ are explained not by greater aromatic stabilization of (**221**) relative to (**213**), but rather by the lower strain energies of phosphorus rings compared to the nitrogen rings (86IC4382). Thus, according to CI-SD 4-31G calculations [82CPL(90)421], the cyclic structure of P_3 proves more stable than the linear structure, whereas for the cyclic and linear isomers of N_3 the relationship between the energies is reversed. In contrast to the relative stabilities of the cyclic, bent and linear isomers of N_3^- , the D_{3h} structure of P_3^- ($^3A'_2$) (**222**) has a lower energy than the C_{2v} bent structure of the singlet state and the linear $D_{\infty h}$ structure ($^1\Sigma_g^+$) of P_3^- (88MI6). As distinct from the aromatic D_{3h} structure of P_3^+ (**221**), the antiaromatic D_{3h} structure of P_3^- ($^3A'_2$ ground state) is more stable by a mere 8.4 kcal/mol than the linear $D_{\infty h}$ structure ($^1\Sigma_g^+$ state)—this has been shown by calculations (88MI6), performed at the same level (MP3/DZ + P//DZ + P) as for the P_3^+ isomers.



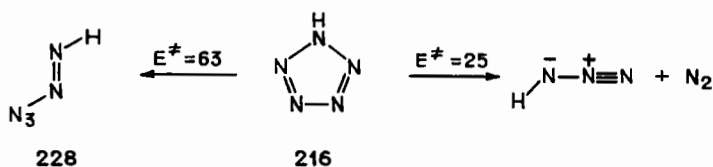
The D_{5h} 6π -electron structure of pentazole anion (**215**) corresponds, according to 3-21G calculations [85CPL(152)402], to a minimum on the PES; note that, unlike the case with hexazine [83JA(105)1760], this minimum is not flat. Structure (**215**) is thermodynamically unstable to decomposition into an azide anion and molecular nitrogen; however, the activation energy of this reaction amounts to 22.3 kcal/mol (MP2SDQ/6-31 + G*//3-21G with ZPVE included) (85MI5). The open-chain isomer of N_5^- , the pentazene anion (**223**), has an energy higher by 68 kcal/mol than the aromatic structure (**215**) (4-31G) (83CJC1435). The activation barrier of the (**215**) \rightarrow (**223**) isomerization amounts to 75 kcal/mol. The results of calculations (83CJC1435; 85MI5) indicate the possibility of the isolation of (**215**) in an ethanol matrix at low temperature or in the form of a $(N_5)M(CO)_3$ complex (with $M = Fe^{2+}$, Mn^+ and Cr), e.g., (**224**), or else in the form of the complex (**225**). For P_5^- , complex (**226**), analogous to (**225**), has been obtained from white phosphorus and $[C_5Me_5Fe(CO)_2]_2$ [87AG(E)59]. According to EHMO calculations (89MI7), complexes containing P_5^- and P_6 rings may, apparently, possess even greater stability than their hydrocarbon analogs. The pentaphosphacyclopentadiene anion

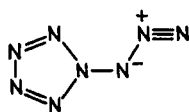


(227) is formed, upon cleavage of white phosphorus with sodium in diglyme (87M15). As judged from the IR and Raman spectra of the NaP_5 solution, the phosphorus five-membered ring is planar and has D_{5h} symmetry [88AG(E)(27)280]. The MNDO (84CJC341) and *ab initio* (89CB2121) calculations indicate that the planar D_{5h} structure (227) corresponds to a mini-

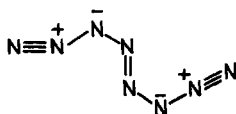


mum on the PES, $R(\text{PP}) = 2.093 \text{ \AA}$, 3-21G* (89CB2121), which is deeper than that for hexaphosphabenzene P_6 [for $\text{P}_5^- \nu(E'_2) = 210 \text{ cm}^{-1}$, whereas for $\text{P}_6 \nu(E_{2u}) = 51 \text{ cm}^{-1}$] (89CB2121). As in the case with the isomers of N_5^- , the 6π -electron planar structure of pentazole (216) that corresponds to a minimum on the PES is more stable by 56 kcal/mol than its acyclic isomer, pentazene (228) (STO-3G, $351 \times 351 \text{ CI}$) (79NJC607). The barrier of the (216) \rightarrow (228) isomerization equals 63 kcal/mol. The energy of pentazole is 8 kcal/mol higher than the sum of energies of NH_3 and N_2 . However, the activation barrier of decomposition of pentazole is 25 kcal/mol (79NJC607). The N_3 -substituted pentazole (229) is more stable by

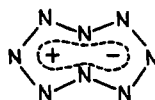




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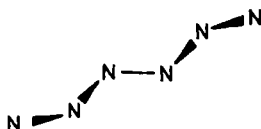


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6.6 kcal/mol than the open-chain form (230) and by 32.8 kcal/mol relative to the bicyclic structure (231) (4-31G//4-31G (86CC959). Thus, the 6π -electron aromatic five-membered nitrogen rings are more stable compared to their open-chain isomer; they are, however, unstable with respect to decomposition into N_3^- (or N_3H) and N_2 fragments).

C. FOUR-MEMBERED AND SIX-MEMBERED NITROGEN AND PHOSPHORUS RINGS

Since aromaticity is decreased with an increase in the ring size, one may expect that the aromatic stabilization energy for N_6 and P_6 will be smaller versus that for N_5^- and P_5^- . Indeed, as has already been noted, N_5^- and P_5^- are characterized by much deeper minima on the PES compared to N_6 and P_6 (85MI5; 89CB2121). Structures N_5^- (215) and N_5H (216) are more stable than their open-chain isomers (223) and (228). By contrast, hexazine is thermodynamically unstable not only with respect to decomposition into 3N_2 [81CPL(83)317; 83JA(105)1760, 83JMS(105)351], but also to isomerization into an open-chain structure N_6 (232) of C_2 symmetry [83JST(105)351; 84JMS(109)391] whose energy is lower by 38.9 kcal/mol than



232

that of hexazine (6-31G) [84JST(109)391]. *Ab initio* calculations show [86CPL(126)43; 89JPC5722] (Table XVIII) that hexazine is more stable than its valence isomers (233)–(236). The difference between the energies of hexaphosphabenzene (237) and the corresponding valence isomer (239) is smaller than that for analogous structures (41) and (234). Moreover, isomer (238) is even slightly more stable than (237) [86CPL(126)43]. Differences between the relative energies of the valence isomers of N_6 and P_6 are explained by the fact that phosphorus, as opposed to nitrogen, is not apt to form double bonds [86CPL(126)43]. This is evidenced by the π -

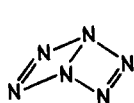
TABLE XVIII
AB INITIO-CALCULATED RELATIVE ENERGIES (IN kcal/mol) OF THE VALENCE ISOMERS N_6
 AND P_6

Structure:	41	233	N_6 234	235	236	$3N_2$
$E_{\text{rel}}, 6-31G^*/3-21G$ [86CPL(126)43]	0	57.4	166.6			
$E_{\text{rel}}, MP2/4-31G^*/4-31G^*$ (89JPC5722)	0	34	120	41	34	-214
Structure:	237	P_6 238	239			$3P_2$
$E_{\text{rel}}, 6-31G^*/3-21G$ [86CPL(126)43]	0	-0.9	1.2 ^a			4.8 ^b

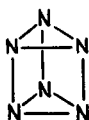
^a According to 6-31G**/6-31G* calculation (89CB2121) $\Delta E(239) - (237) = -24 \text{ kcal/mol}$.

^b MP3/6-31G**/6-31G* calculations [86CPL(126)43].

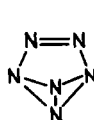
bond strengths for $NH=NH$ and $HP=PH$, already mentioned above (63.5 and 36 kcal/mol, respectively) (86IC248) as well as by the differences between the bond energies ($P=P$) - 2($P-P$) and ($N=N$) - 2($N-N$) equal, respectively, to -17.2 and 19.5 kcal/mol estimated from calculated energies of the dimerizations $2PH=PH \rightarrow \text{cyclo } (PH)_4$ and $2NH=NH \rightarrow \text{cyclo } (NH)_4$ (6-31G**/3-21G) [86CPL(126)43]; hence these interconversions will have to overcome considerable activation barriers.



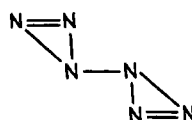
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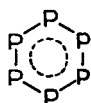
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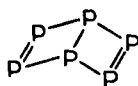
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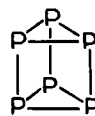
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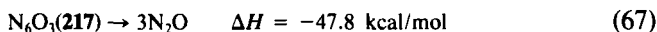
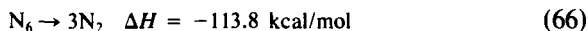
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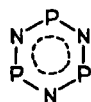
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As contrasted to hexazine, which is thermodynamically unstable to decomposition into $3N_2$ (activation energy is 1.3 kcal/mol) [83JA(105)-1760], phosphabenzene is stable against decomposition into $3P_2$ [86CC383, 86CPL(126)43] (Table XVIII). The activation barrier amounts in this case to 20.2 kcal/mol (MP3/6-31G**/6-31G*) [86CPL(126)43]. Hexazine can be rendered more stable toward decomposition (66) through formation of derivatives of type (217), such as N_6O_3 (88KGS250, 88ZOR2486), as is

demonstrated by the comparison of MNDO-calculated ΔH s of reactions (66) and (67) (88ZOR2486).



Structure P_3N_3 (240), obtained by co-condensation of PN in an excess of argon at 20 K [77SA853; 89CPL(161)179], proves stable against decomposition into 3PN ($\Delta E = 93.4 \text{ kcal/mol}$, *ab initio* calculation) [89CPL(161)179].



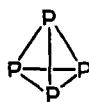
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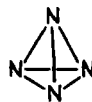
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As has already been mentioned the antiaromatic character of tetrazete N_4 (61) is even more strongly pronounced than in the case of cyclobutadiene—this was shown by calculations of TRE [88IJC(A)653] and HSE (87ZSK28). (61) may be stabilized in the form of the complex $\text{N}_4 \cdot \text{Fe}(\text{CO})_3$ (69ZSK159). Tetraphosphacyclobutadiene (241) and tetraarsacyclobutadiene (242) were isolated in an analogous form (89JOMC35, and the literature cited therein). Whereas the polycyclic valence isomers of P_6 are, in contrast to the valence isomers of hexazine (41), close in stability to hexaphosphabenzene (Table XVIII), structure (241) possesses an even greater energy than the tetrahedral structure (243) (Table XIX).

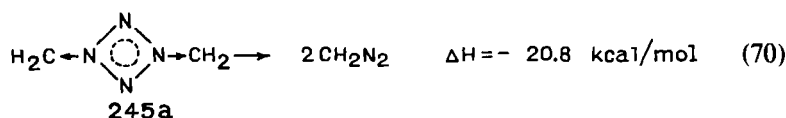
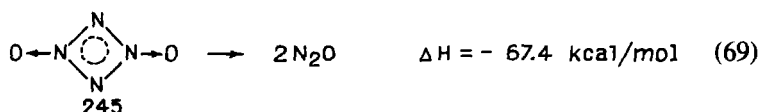
Tetrazete (61) is more stable than tetraazatetrahedrane (244) (Table XIX); (61) is however, unstable to decomposition into 2N_2 , as distinct from P_4 (241) for which the decomposition into 2N_2 is endothermic. The

TABLE XIX
RELATIVE ENERGIES OF D_{2h} AND T_d STRUCTURES OF N_4 AND P_4 AND ENERGIES (IN kcal/mol) OF DECOMPOSITION OF D_{2h} STRUCTURES X_4 INTO 2X_2 ($\text{X} = \text{N}, \text{P}$)

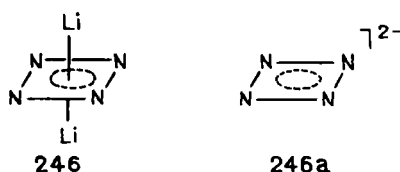
	N_4		P_4
	MNDO (87ZSK28)	6-31G**/4-31G (87ZSK28)	MNDO (84CJC341)
$\Delta E(D_{2h} - T_d)$	-37.5	-20.0	25.4
$\Delta E(\text{X}_4(D_{2h}) \rightarrow \text{X}_2)$	-131.2	-214.6	19.8 ^a

^a Experimental value of ΔH for $\text{P}_4(T_d) \rightarrow 2\text{P}_2$ decomposition is 55 kcal/mol (84IC4365); MP4/6-31G (2df)//MP3/6-31G*-calculated $\Delta E(\text{P}_4(T_d) \rightarrow 2\text{P}_2) = 56.7 \text{ kcal/mol}$ (85CPL219).

instability of tetrazete with respect to decomposition (68) can be deduced, as pointed out above, through formation of its derivatives (245) and (245a) (ΔH of the following reactions were calculated by the MNDO method (88KGS250):



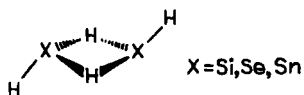
According to 6-31G* calculations (90JA4155), the square geometry of the N_4 fragment may be stabilized in the D_{4h} structure of tetrazete dianion with two Li^+ counteranions (246) that corresponds to a minimum on the PES. Also, the planar square 6π -electron structure corresponds to a minimum on the PES, as judged from *ab initio* calculations with the 6-31+G* basis set (90JA4155).



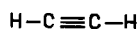
The foregoing evidence clearly shows that the relative stability of the valence isomers of N_6 , N_4 , P_6 , and P_4 and, in particular, the stability against decomposition into two-atom molecules are in the first place regulated by the specific features of the σ -system; furthermore, they are related to the reduced strength of the $\text{P}=\text{P}$ π -bonds. Is the assertion now justified that the aromaticity and antiaromaticity effects do not play a leading role in the chemistry of the main-group elements of the second and subsequent rows? The correctness of such a claim may be tested by examining the analogs of annulenes and conjugated monocyclic ions formed by the 14 group elements Si, Ge, and Sn, to which we turn in the next section.

VI. Aromaticity Concept in the Chemistry of Group 14 Elements next to Carbon

An analysis of the electronic and molecular structure of the compounds with multiple bonds formed by main-group elements of the second and higher rows points to some important differences distinguishing these compounds from those of the first-row elements [84AG(E)272; 87JST1]. The structures of these molecules, often inconsistent with the classical stereochemical notions, as in Si_2H_2 (86JA270; 89JPC118) and X_2H_4 (**247a**) (90JA2130), used to be regarded as anomalous compared with their carbon analogs (see **247** and **248**). However, it would, apparently, be more appropriate to consider as "abnormal" the strong π -bonds and corresponding

**247****247a**

X = Si, Se, Sn

**248**

structures formed by carbon and other first-row elements (N,O) [84AG(E)272]. This departure from the rule can be accounted for by the specificity of these elements, which in contrast to those placed in the second row of the Periodic Table, have no inner *p*-orbitals [84AG(E)272; 87JST1]. Thus, as one goes from carbon compounds to isoelectronic compounds of the heavier group 14 elements, a substantial revision of the commonly used stereochemical and some other theoretical models is required. In this connection, of particular interest is the question to what extent the concept of aromaticity may be applied to cover the properties of compounds formed by such 14 group elements as Si, Ge, and Sn.

A. AROMATIC STABILIZATION OF THE π -BONDS $\text{C}=\text{X}$ AND $\text{X}=\text{X}$ ($\text{X} = \text{Si}, \text{G} = \text{e}, \text{Sn}$)

The aromaticity concept has proved to be quite useful in the chemistry of the group 14 elements since it is in its terms that one of the approaches to the stabilization of the π -bonds $\text{C}=\text{X}$ and $\text{X}=\text{X}$ ($\text{X} = \text{Si}, \text{Ge}, \text{Sn}$) is formulated.

We have already noted that the great strength of the π -bonds in organic compounds should be regarded as a special attribute of the first-row elements [84AG(E)272; 87JST1]. This is evidenced by a comparison between the energies of the $\text{C}=\text{X}$ bonds ($\text{X} = \text{C}, \text{Si}, \text{Ge}, \text{Sn}$) and that of $\text{X}=\text{X}$ ($\text{X} = \text{C}, \text{Si}$) (see Table XX). Thus, the π -bonds formed by the Si, Ge, and

TABLE XX
ENERGIES OF π -BONDS IN ETHYLENE AND ITS ANALOGS H_2CXH_2 ($X = C, Si, Ge, Sn$)
DETERMINED BY DIFFERENT METHODS (IN kcal/mol)

Structure	MP2/3-21G* (86M18)		MP2/6-31G* (86M18)		MP4/6-31G* ^a (88JA2105)		Exper.
$H_2C=CH_2$	64 ^b	(67) ^c	66 ^{b,d}	(68) ^c	69.6	65	(56JCP315)
$H_2C=SiH_2$	35	(35)	36	(35)	36.1	38	(81ACR246; 82JA4329)
$H_2C=GeH_2$	31	(31)					
$H_2C=SnH_2$	19	(19)					
$H_2Si=SiH_2$					24.2	26 ^e	

^a Including ZPE.

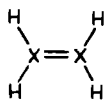
^b From rotational barrier.

^c Values in parentheses have been obtained from disproportionations energies for reactions $H_2X-CH_3 + H_2X=CH_2 \rightarrow H_2X-CH_3 + H_3X-CH_2$ (86M18).

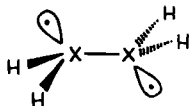
^d According to MP4/6-31G//3-21G* calculations [using (12s,9p)/(6s,5p) basis set for Si] (87JA5217) and available experimental values, the recommended bond strengths are 65(C=C), 38(C=Si), 25 (Si=Si) kcal/mol.

^e Estimated from the experimental *cis-trans* isomerization barrier in a substituted disilene (84M16).

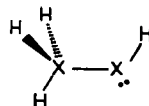
Sn atoms are far less strong than those of carbon and distortions in which a *trans*-pyramidalization of Si, Ge, and Sn centers takes place may prove to be energetically favored (**250**), (**251**). The type (**251**) structures are stabilized through σ -conjugation, which can compensate the loss of the relatively weak π -bond in compounds with $X = Si, Ge, Sn$ (84JA6773). Indeed, both theoretical [82CC1407; 86CPL(130)115, 86JCS(D)2387; 87JA4141; 88JMS(163)207; 89JA5916; 90JA1039, 90JA2130] and experimental [84JOM(273)141, 84M113; 85CRV419; 87AG(E)1201, 87PAC1011; 90CRV283] studies reveal *trans*-pyramidalized structures of pseudo-olefines H_2XXH_2 ($X = Si, Ge, Sn$). Note that for Sn_2H_4 the *trans*-bridged structure (**247a**) is more stable than the bent structure (**250**), whereas planar structure (**249**) is found (90JA2130) to be a saddle point. For $X=C$, structure (**250**) is a saddle point on the PES (90JA2130). The specificity of the $1s, 2p, 3d$, etc., orbitals is manifested in that the orbital radius R_{max} (the distance between the nucleus and the main maximum of the radial function of distribution) is, for the $2s$ carbon orbital, influenced by the $1s$ AO and turns out to be even greater (0.620 Å) than in the case of the $2p$ AO



249



250



251

(0.596 Å) (65JCP4116). [This effect has been termed "primogenic repulsion" in reference to the $3d$ and $4d$ orbitals [79ZN(A)214]. Whereas for C $\Delta R_{\max} = (R_{\max}(np) - R_{\max}(ns))$ equals -0.024 Å, for Si it is 0.164 Å, for Ge 0.204 Å and for Sn 0.213 Å.] Thus, for the np AOs of Si, Ge, and Sn a diminished propensity compared to the corresponding $2p$ AOs of carbon toward participation in bond-making is characteristic. This is reflected in the formation of structures in which the Si atom is dicoordinated and the nonbonding electrons are accommodated in the s -orbital (86JA270). This means that the energy of the structure of type (251) can be only slightly higher than that of the type (250) structure, which has been confirmed by both theoretical [86CPL(130)115, 86JA270; 87JA4141] and experimental [87JPC5011; 88JA24] data for Si_2H_4 and CH_2SiH_2 .

The aromatic stabilization of the planar bond configuration may qualitatively be interpreted in terms of a model of the electronic structure of pseudo-olefines (87JA5303), in which the planar structure (249) is viewed as resulting from the interaction between two analogs of carbene XH_2 in the triplet state, whereas the *trans*-pyramidalized structure (250) results from that between two carbene-type units XH_2 in the singlet state.



The ground state for silylene SiH_2 , germylene GeH_2 , and stannylene SnH_2 is a singlet (89RCR1067) and, as shown in Carter and Goddard (86JPC998), the strength of the $(\pi + \sigma)$ -bond correlates with the value of $\Delta E_{\text{S-T}}$ of the XH_2 fragments. Hence, it should be expected that the relative stability of the structure (250), compared to that of the planar structure (249), will grow in the order Si–Ge–Sn. According to Trinquier and Malrieu (87JA5303), the structures (249) and (250) will be close in energy, provided the sum of the values of $-\Delta E_{\text{S-T}}$ of the fragments is equal to approximately $\frac{1}{2}E_{\pi+\sigma}$ where $E_{\pi+\sigma}$ is the energy of the $(\pi + \sigma)$ bond:

$$-\left(\sum \Delta E_{\text{S-T}}\right) \sim (1/2)E_{\pi+\sigma} \quad (71)$$

However, the *trans*-pyramidalized structure (250), as opposed to structure (249), will possess lower energy than (249) if inequality (72) is satisfied:

$$-\left(\sum \Delta E_{\text{S-T}}\right) > (1/2)E_{\pi+\sigma} \quad (72)$$

The lowering of the energy of the $1b_u$ orbital, which is formed upon mixing in of the π -orbital to the σ^* -orbital resulting in the distortion (249) \rightarrow (250), serves as a main factor determining the energy preference of structure (250) over structure (249)—see Fig. 5.

In the $H_2X=XH_2$ series ($X = C, Si, Ge, Sn$) the difference between the energies of the σ - and π^* -orbitals changes but slightly. As a result, the energy difference between the π - and σ^* -orbitals becomes crucial. The latter difference determines the effectiveness of their mixing in the distortion into structure (250) and, consequently, the possibility of such a distortion.

Thus, the stabilization of the π -orbital due to the inclusion of an $X=Y$ fragment ($X, Y = C, Si, Ge, Sn$) into the conjugated (aromatic) system will lead to an increase in the difference between the energies of the π - and σ^* -orbitals and, ultimately, the planar structure will be stable to the pyramidalization of the Si, Ge, Sn -centered bonds. Thus, the inclusion of the double bond $X=Y$ ($X, Y = C, Si, Ge, Sn$) into a conjugated system affording an aromatic molecule is one of the ways of stabilizing this bonding, particularly, with respect to the pyramidalization of these centers.

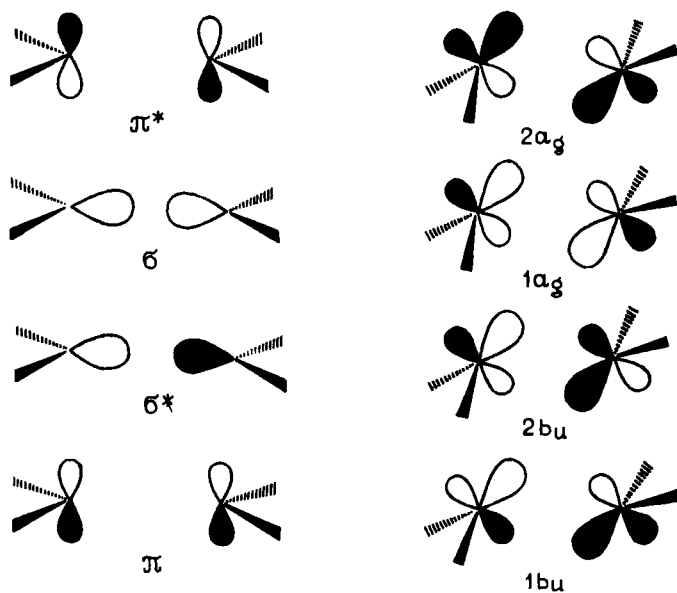
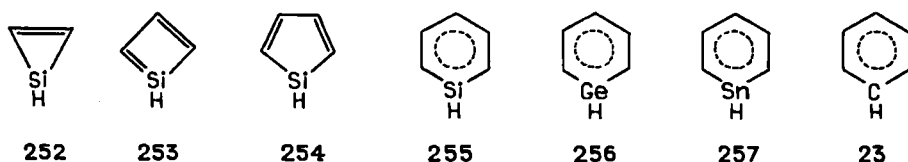


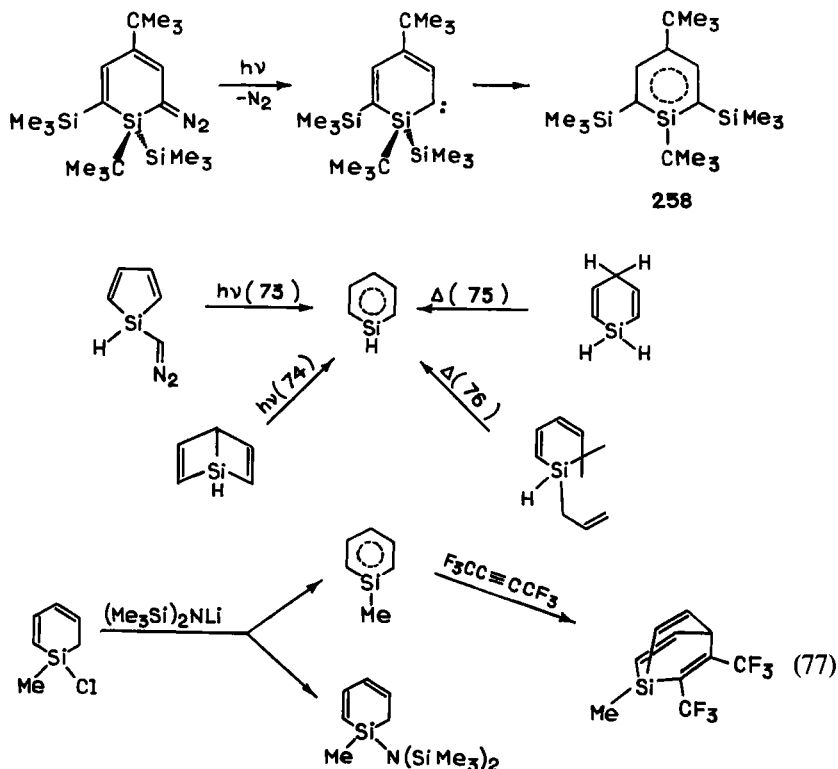
FIG. 5. Transformation of the orbitals of the π - and σ -bonds in $H_2X=XH_2$ due to the pyramidalization of atoms X ($X = C, Si, Ge, Sn$) [adapted from Shin *et al.* (88JA24)].

B. Si-, Ge-, Sn-CONTAINING ANNULENES AND MONOCYCLIC CONJUGATED IONS

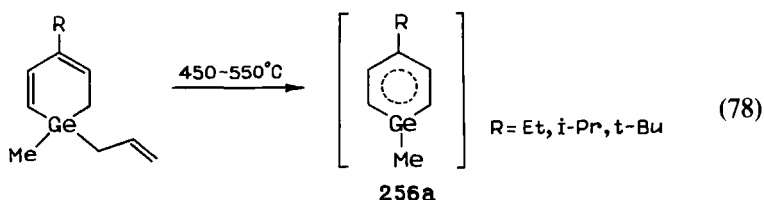
So far practically no silaaromatic compounds stable enough to be isolated preparatively have been obtained. The available data have been derived through investigations in the gas phase or by using the matrix isolation method [80AG(E)52; 85CRV419; 86MI11, 86PAC95; 89-



AG(E)1627, 89MI8]. The only known exception is 1,4-di-*tert*-butyl-2,6-bis(trimethylsilyl)silabenzene, (**258**) which is stable in solution at -100°C [88AG(E)(27)963]. For generating silabenzene photochemical reactions



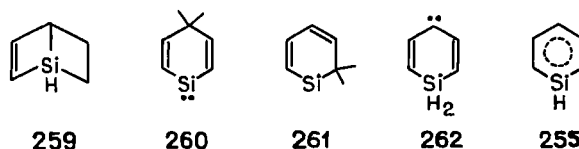
(73), (74) as well as gas-phase thermolysis (75), (76) were employed [85CRV419; 89JMS(188)223]. Silabenzene was also identified as a reactive intermediate by obtaining a number of its adducts, such as that in reaction (77) (77JA5199; 85CRV419; 86PAC95). The 1,4-dialkylgermabenzenes generated by gas-phase pyrolysis have been spectroscopically detected [82AG(E)221; also see 90CRV283].



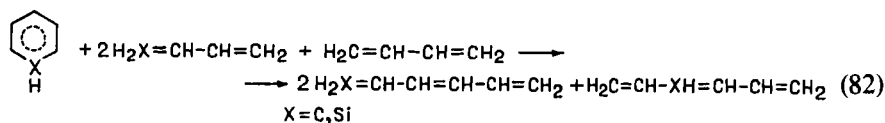
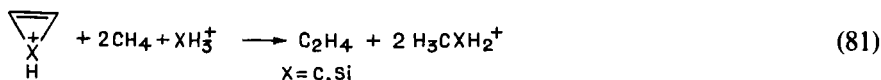
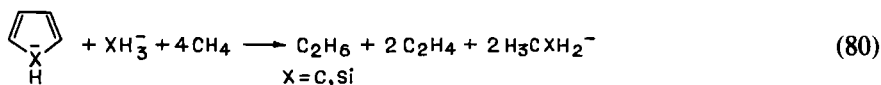
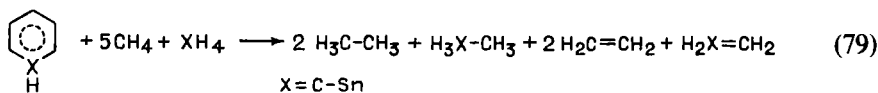
Both semiempirical (82JST77) and *ab initio* (78JA6499; 79JOM21; 83JOC3453; 88MI1) calculations on silabenzene indicate a planar geometry. The calculated electron distribution shows that the Si atom should be attacked first by nucleophiles (79JOM21). According to calculations [78JA6499; 83JA(105)4972, 83JOC3453], the CSi bond length in silabenzene [1.722 Å (STO-3G) (83JOC3453); 1.760 (3-21G*) (88JA4204)] is intermediate between the lengths of the SiC bonds in silaethene and methylsilane (1.64 Å), calculated at the same computational level; for experimental data on $\text{Me}_2\text{Si}=\text{CH}_2$ see Schaefer (82ACR283) and Gutowsky *et al.* (89JA1901). This points to the presence of π -conjugation. Thus, by its structural characteristics silabenzene may be classified as a benzene analog. The analogy is seen also in such characteristics as UV spectra that are typical of perturbed benzene (85CRV419) and the magnitude of π -ionization energies [84JOM(271)145]. The experimental values of these energies (11.31, 9.46, and 8.11 eV) agree well with those derived by use of the correlation of the π -ionization energies of heterobenzenes $\text{C}_5\text{H}_5\text{X}$ and the ionization energies ($^4\text{S}_{3/2} \rightarrow ^3\text{P}_0$) of the perturbing atom X [89AG(E)1627].

In the lower triplet state, the silabenzene molecule retains its planar structure whose energy is higher by 107 kcal/mol than that of the structure of the singlet ground state (STO-3G) (78JA6499). Like benzene, silabenzene is more stable than its isomers (259)–(262) by, respectively, 38.4, 18.0, 23.5, and 37.2 kcal/mol [37.2 kcal/mol for the triplet state of (262)] and by 72.5 for the singlet (3-21G*//STO-3G) (83JOC3453). A greater stability of silabenzene (255), compared to (260) and (261), may be attributed to the aromaticity of (254) (83JOC3453), since π -conjugation of the diene fragment with the p_π orbital of silicon is also possible for the (260),

(261) molecules. So the stabilization of (255) relative to (260) and (261) (18–23.5 kcal/mol) may be regarded as a consequence of aromaticity (83JOC3453). The carbene structure (262) is the least stable among (255), (259)–(261), which is in parallel with the fact that silylmethylene $\text{H}_3\text{C}-\text{SiH}$ is also energy-unfavorable with respect to methylsilylene $\text{H}_3\text{C}-\text{Si}$ and



silene $\text{H}_2\text{Si}=\text{CH}_2$ (86JA270). More rigorous estimates of the aromaticity of silabenzene (255), as well as of germa- and stannabenzenes, may be derived from the calculation of the energies of isodesmic (79)–(81) and hyperhomodesmotic (82) reactions (Tables VIII and XXI). As is evident



from Table XXI (the value of R), the stabilization of silabenzene amounts to 80% of benzene's aromatic stabilization. According to the values of HHSE, the stabilization comes to 69% of the aromatic stabilization of benzene, whereas for germa- and stannabenzenes this percentage is 64 and 47, respectively (Table XXI). Thus, a comparison among the aromaticity stabilization energies of the molecules (255)–(257) bears witness to a sharp change in the aromatic stability on going from benzene (22) to silabenzene (255) and then from germabenzene (256) to stannabenzene (257) (88JA4204). Although the values of ISE and HHSE (Table XXI) point to a similarity in the aromatic character of sila- and germabenzene,

TABLE XXI
AB INITIO-CALCULATED ENERGIES OF THE ISODESMIC REACTIONS (79)–(81) (ISE) AND
 HYPERHOMODESMOTIC REACTIONS (82) (HHSE) (IN kcal/mol)

Reaction	STO-2G [83JA(105)4972]		3-21G [83JA(105)4972]		3-21G* (88JA4204)	
	ΔE	R^a	ΔE	R	ΔE	R
(79)						
X = C	73		59		61.27 ^b (25.99) ^c	
X = Si	61	0.84	47	0.80	46.84 (17.97)	0.76 (0.69)
X = Ge					46.32 (16.75)	0.76 (0.64)
X = Sn					42.84 (12.20)	0.70 (0.47)
(80)						
X = C	102		87			
X = Si	25	0.24	23	0.26		
(81)						
X = C	–10		–24			
X = Si	–30	3.0 ^d	–57	2.37		

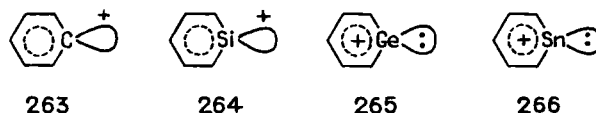
^a R is the ratio $\Delta E(X = \text{Si})/E(X = \text{C})$.

^b Corrected for scaled ZPVE.

^c HHSE (82) is given in parentheses.

^d Destabilization (ISE < 0); the values of ISE corrected for strain energy using ISEs of cyclopropene and silacyclopropene show the stabilization of C_3H_3^+ , but the destabilization of silacyclopropenyl cation (88MI1).

some essential differences in the manifestation of aromaticity of the six-membered rings (C_5Si) and (C_5Ge) are revealed through calculations on cations (263)–(266). The MNDO calculations (90MI3, 90MI4) with the use of a modified parametrization for Si (86MI7) have shown that whereas



for the silaphenyl cation (264) the planar aromatic 6π -electronic structure of C_{2v} symmetry has, like the phenyl cation (263), a lower energy than the antiaromatic 4π -electronic structure, in the case of the germaphenyl cation (265), the latter structure is, on the contrary, more stable (Table XXII).

Because of the aromaticity effects, the electronic ground state of the phenyl cation C_6H_5^+ (263) is singlet 1A_1 (6π -electronic structure) [88-

TABLE XXII
MNDO-CALCULATED VALUES OF THE SINGLET-
TRIPLET GAP ΔE_{S-T} AND DIFFERENCES BETWEEN
THE ENERGIES OF THE 6π - AND 4π -ELECTRON
PLANAR STRUCTURES $C_5H_5X^+$ ($X = C, Si, Ge, Sn$)
OF C_{2v} SYMMETRY [84JOM(271)145]
 $\Delta E(^1A_1, 6\pi) - (^1A_1, 4\pi)$ (IN kcal/mol)

Structure	ΔE_{S-T}	$\Delta E (6\pi-4\pi)$
263 , $X = C$	-3.0^a	-56.2
264 , $X = Si$	21.6	-4.6
265 , $X = Ge$	24.0^b	17.2^b
266 , $X = Sn$	-20.4^c	—

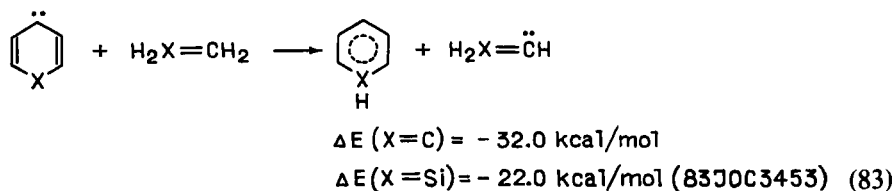
^a According to MCSCF 6-31G**/STO-3G calculations [88CPL(153)309] ΔE_{S-T} (**263**) = -4.9 kcal/mol.

^b The 4π electron planar structure of singlet 1A_1 state is more stable than the 6π electron structure (1A_1).

^c The $^1A_1 (4\pi)$ state is the ground state of (**266**).



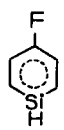
CPL(153)309] rather than triplet 3B_1 as in the case of methylene (85T-1531; 89UK1067). The lowering of the aromatic stabilization from the sila- to the germaphenyl cations is seen not only in a change in the value of the difference between the energies of the 6π - and 4π -electronic structures [critical change for (**265**)], but also in the fact that the electronic ground states for (**264**) and (**265**) have been found to be a triplet (Table XXII) (see also the *ab initio* calculations) (80JOC1608). The diminishing role of the antiaromatic destabilization effects in the series of 4π -electronic structures $C_5H_5X^+$ $X=C, Si, Ge, Sn$) leads to the conclusion that the electronic ground state of the stannaphenyl cation (**266**) is a singlet, as in the case of the phenyl cation (**263**). Unlike the latter, however, structure (**266**) has the 4π -electronic ground state (formally antiaromatic) (see Table XXII).

An estimate of the aromatic stabilization energy of silabenzene, based on the calculation of the ISE (STO-3G basis set) (78JA6499), concludes that its value is 2/3 of the benzene stabilization energy. Possible ap-



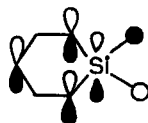
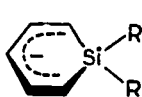
proaches to stabilization of the silabenzene structure through introduction of an appropriate substituent have been discussed in Carter and Goddard [86JPC998] and Mizoguchi [88JMS(181)245]. It can be achieved by π -accepting substituents at the *ortho*- or *para*-carbon atoms, σ -accepting substituents at the *ortho*- and *meta*-carbon atoms, and π -donating ones at the Si atom (77T3061). According to the calculations of ISE (3-21//STO-2G) [88JST(181)245], fluorosilabenzene, C_5H_5SiF , possesses the most and carboxysilabenzene, $C_5H_5SiCOOH$, the least relative stability among the structures C_5H_5SiX ($X = H, F, Cl, OH, SH, NH_2, PH_2, CN, NO_2, CH_3, SiH_3, OCH_3$, and $COOH$). The ISE of *meta*-fluorosilabenzene amounts to 117.1 and 93.3% of that of, respectively, silabenzene and benzene. The greater stability of 3-fluorosilabenzene (**267**) over 2- and 4-fluorobenzene (**268**), (**269**) is explained by the fact that fluorine, when in position 3, does not disturb markedly the electron distribution in silabenzene [88JST(181)245].

The relatively great stability of 3-fluorosilabenzene is consistent with its significant aromatic character, which can be estimated from the value of ISEs and that of R , i.e., the ratio between ISEs for fluorosilabenzene and the corresponding (*o,m,p*) isomer of fluorobenzene

			
	267	268	269
$E_{rel}(3-21G // STO-2G), kcal/mol$	0	10.0	2.9
ISE (kcal/mol)	55.9	48.1	53.0
$R = \frac{ISE(X = Si)}{ISE(X = C)} (88M11)$	0.84	0.73	0.80

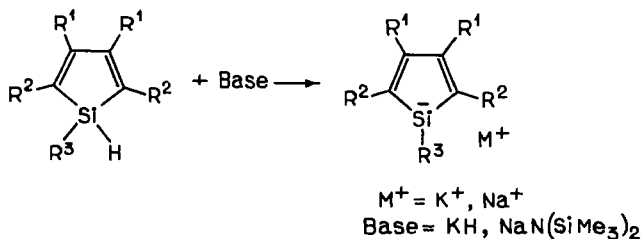
The silacyclohexadienyl anions $C_5H_5SiR_2$ can be obtained by deprotonation of the corresponding silacyclohexadienes [84JOM(260)129]. The X-ray crystal structure and NMR and IR investigations of the crown ether complexes of lithium silacyclohexadienides $Li(12\text{-crown-}4)_2Me_2SiC_5H_5$ and $Li(12\text{-crown-}4)_2t\text{-Bu(H)SiC}_5H_5$ (shortening of the Si—C bond lengths as against those in silacyclohexadiene systems, NMR signals for the ring-carbon hydrogens are at comparatively low field and some other features) indicate that the silacyclohexadienide anion $C_5H_5SiH_2^-$ possesses a flat ring structure and a so-called quasiaromatic character (90JA4841). Owing to the hyperconjugation effect of the pentadienide fragment HOMO and the σ^* SiR_2 orbital, the endocyclic Si—C bonds in the silacyclohexadie-

nide anion have a somewhat double-bond character, which admits the presence of cyclic π -electron delocalization.

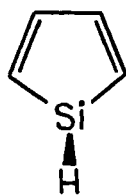


HOMO of $\text{C}_5\text{H}_5\text{SiH}_2^-$

Ab initio calculations of the energies of the isodesmic reactions (80) and (81) have shown that the aromatic stabilization energy of the silacyclopentadienide anion (**254**) is a mere 23–25% of that of the cyclopentadienide anion $(\text{CH})_5^-$ [83JA(105)4972]. The silacyclopentenyl cation is altogether destabilized [83JA(105)4972]. Substituted silacyclopentadienide anions have been obtained in good yield by treating 1-hydridosiloles with strong nonnucleophilic bases in tetrahydrofuran (90CRV265). The lower value of ISE for $\text{C}_4\text{H}_4\text{SiH}^-$ (**254**) is found because delocalization of the negative



charge in (**254**) onto the carbon atoms is impeded, being associated with an increase in the order of the C—Si bonds and a decrease in the CC bond order [83JA(105)4972]. Moreover, as the *ab initio* 6-31G*//6-31G* calculations have shown (86JOC5028), the planar C_{2v} structure (**254**) does not correspond to a minimum on the PES but rather to the transition state of pyramidal inversion of the nonplanar C_s structure (**270**), whose energy

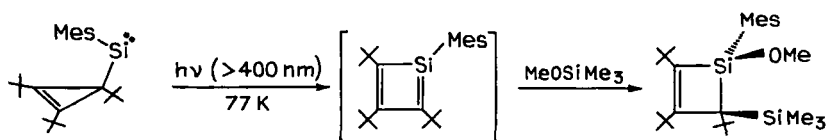


270

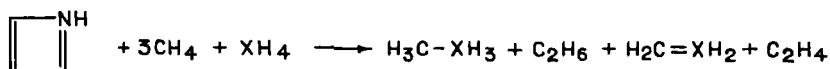
is lower by 16.2 kcal/mol. The length of the C—Si bond is in (270) considerably greater (1.924 Å) than in (254) (1.788 Å). The CC bonds in (254) have approximately equal lengths—1.401 and 1.405 Å. By contrast in (270) they alternate substantially (1.341 and 1.472 Å) (86JOC5028). Such a ring geometry points to a lack or insignificance of conjugation effects.

The lowering of the aromatic stabilization energy of silabenzene, compared to benzene, leads one to expect that the energy of the antiaromatic stabilization of silacyclobutadiene (253) would be lower than in the case of cyclobutadiene.

Recently the formation of substituted silacyclobutadiene has been reported in the photolysis of 2-mesityl-2-(1,2,3-tri-*tert*-butylcyclopropenyl) hexamethyltrisilane (88JA1315).



According to the *ab initio* calculations (80CC1131; 84MI4; 87MI6), the silacyclobutadiene molecule has a planar structure of symmetry C_s with alternating bond lengths: $R(C=Si)=1.685$ Å; $R(C-Si)=1.884$ Å; $R(C=C)=1.333$ Å; and $R(C-C)=1.544$ Å (6-31G**/6-31G*) (87MI6). The structure of the lower triplet state has an energy higher by 7.9 kcal/mol than the singlet state (DZ basis set, MC SCF) (84MI4). Silacyclobutadiene is ~ 5 kcal/mol less stable than its decomposition products, i.e., acetylene and 1-silavinylidene (84MI4); however, this reaction is symmetry-forbidden. A calculation of the isodesmic reaction (84) energy has shown that the antiaromatic destabilization on silacyclobutadiene amounts to 78.4% of that of cyclobutadiene (6-31G**/3-21G) (ΔE is given in kcal/mol) (80CC1131). [This value should be regarded as approximate since $\Delta E(X=C)$ was calculated (75JA6941) with the 6-31G* basis set, but with the geometry optimized using 4-31G, whereas 3-21G was used for $X=Si$ (80CC1131).] The energy of silatetrahedrane (with C_{3v} symmetry) is higher by 32.0 kcal/mol (6-31G**/6-31G*) (87MI6) than that of silacyclobutadiene and its experimental detection appears unrealistic.

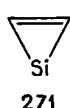


$$E(X=C) = -67.9 \text{ (75JA6941)}$$

$$E(X=Si) = -53.3 \text{ (80CC1131)} \quad (84)$$

C. SILACYCLOPROPENYLIDENE AND SILACYCLOPENTADIENYLIDENE

According to *ab initio* calculations (86JA2169), the planar C_{2v} structure of silacyclopropenylidene (**271**) corresponds to a global minimum on the PES, being more stable by 17 and 22 kcal/mol (DZ + P,CI) than that of, respectively, vinylidenesilene and silyleneacetylene. The length of the CC bond in (**271**) is 1.343 Å, whereas that of the CSi bond amounts to 1.806 Å, which is a value intermediate between those of the ordinary (1.92 Å) and the double (1.71 Å) CSi bonds. These data indicate that there is considerable conjugation between the π -orbital of the CC bond and the vacant p -orbital of the Si atom (86JA2169).



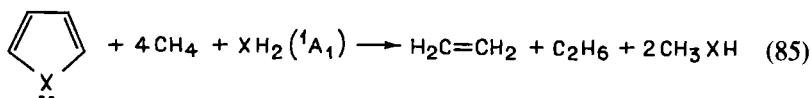
272 (X=C); 273 (X=Si);
274 (X=Ge); 275 (X=Sn)

The MNDO calculations on sila-, germa-, and stannacyclopentadienylidenes have shown that whereas for cyclopentadienylidene (**272**) the energies of the antiaromatic 4π - and the aromatic 6π -electron structures are close in value (89UK1067), in the (**273**)–(**275**) series the 6π -electron structures are quite noticeably destabilized (Table XXIII). Unlike (**272**), the electronic ground state of compounds (**273**)–(**275**) correspond to minima on the PES. These results point to the diminished role of antiaromatic destabilization in the 4π -electron structure (**273**)–(**275**), as opposed to (**272**). It should therefore be expected that these molecules would be more stable than (**272**). This has indeed been confirmed by our calculation on the heats of the isodesmic reaction (85) (Table XXIII).

TABLE XXIII
MNDO-CALCULATED ISE [Eq.(85)], ΔE_{S-T} AND ENERGY
DIFFERENCES FOR 6π - AND 4π -ELECTRON STRUCTURES C_4H_4X
(X = C,Si,Ge,Sn) (87MI6) (IN kcal/mol)

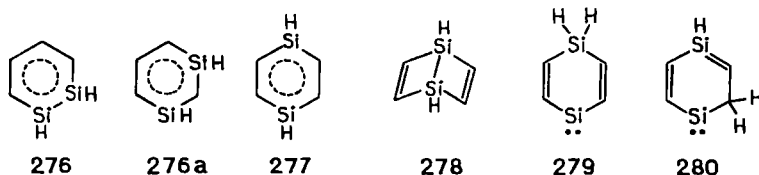
Structure	ISE	ΔE_{S-T}	$\Delta E(6\pi - 4\pi)$
272 , X = C	-11.7	21.6 (21.0) ^a	5.9 (6.4) ^a
273 , X = Si	8.9	-9.6	60.2
274 , X = Ge	10.4	-4.5	72.1
275 , X = Sn	5.1	-23.1	123.6

^a The values calculated for nonplanar C_s structure of cyclopentadienylidene are given in parentheses (75JA6941).



D. DISILABENZENE AND DISILACYCLOBUTADIENE

The 1,2-disilabenzene molecule (**276**) affords an opportunity to trace the effects of stabilization of the Si=Si bond when it is included in the aromatic system. The *ab initio* calculations [84JOM(271)369] have shown that even though the Si atoms in a disilene molecule are pyramidalized (86JA270; 87JA4141), the planar structure (**276**) corresponds to a minimum on the PES. A comparison of the calculated C—Si and C—C bond lengths with the corresponding average lengths of the ordinary and double CC and CSi bonds has indicated considerable π -conjugation in (**276**) [84JOM-(271)369].

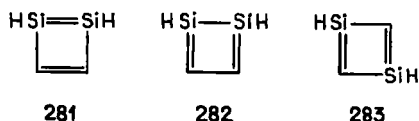


E_{relative} (3-21G//STO-2G) (kcal/mol)	2.0 (276)	0 (276a)	10.8 (277)
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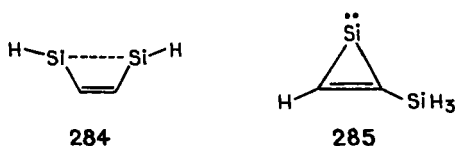
R	0.38 (276)	0.80 (276a)	0.62 (277)
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$R = \text{ISE}(\text{X} = \text{Si})/\text{ISE}(\text{X} = \text{C})$

Of the (**276**)–(**277**) structures, the 1,3-isomer (**276a**) is the most stable. The calculation of ISE also shows that the 1,3-isomer possesses a greater value for the energy of aromatic stabilization (see the values of R). The preparation of hexamethyl-1,4-disilabenzene has been reported (82-JA6884). According to *ab initio* calculations on 1,4-disilabenzene (**277**) and its isomers (**278**)–(**280**) (85JOM51), structure (**277**) is more stable than its valence isomers (**278**) (by 5.9 kcal/mol, 3-21G*//STO-3G) and (**280**) (by 21.0 kcal/mol, STO-3G//STO-3G). On the other hand, structure (**279**) possesses an energy lower by 9.9 kcal/mol than (**277**) (3-21G*//STO-3G). Whereas for aromatic 1,2-disilabenzene (**278**) a stabilization of the Si=Si bond is observed with respect to the pyramidalization of the Si atoms, the planar structure of antiaromatic 3,4-disilacyclobuta-1,3-diene (**281**) does not correspond, according to the *ab initio* calculations (84MI5), to a mini-

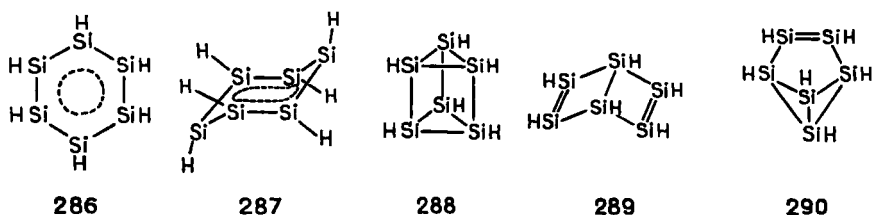


mum on the PES. This is also the case with structure (280) (both correspond to the second-order saddle points on the $C_2H_2Si_2H_2$ PES). These unstable structures relax without a barrier to the stable structure (284). The structure of 2,4-disilacyclobuta-1,3-diene (283) does correspond to a minimum on the PES; its energy is, however, higher by 49.7 kcal/mol (MP3/6-31G**/3-21G) than that of (285). The above difference is reduced by 20.3–30.8 kcal/mol when the CI is included. But even so, the (283) structure remains one of the least stable isomers of $C_2Si_2H_4$ (84MI5)

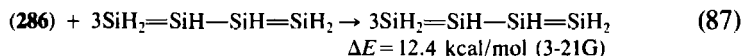
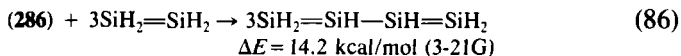


E. HEXASILABENZENE AND TETRASILACYCLOBUTADIENE

The above-considered results of theoretical and experimental studies on sila- and disilabenzenes suggest that they possess an aromatic stabilization energy that is lower in comparison with benzene. Will the manifestations of aromaticity be characteristic for hexasilabenzene (286) and, if so, to what degree? Analogous 6π -electron structures of D_{6h} symmetry of hexaazabenzene N_6 and hexaphosphabenzene P_6 correspond, as *ab initio* calculations have shown, to minima on the PES. However, the former species is unstable being subject to the decomposition $N_6 \rightarrow 3N_2$, whereas the latter is less stable than the Dewar structure P_6 [86CPL(126)43]. Keeping in mind the stabilizing effect of the X—H bonds (74JA4753) one may expect that hexasilabenzene will not be so unstable.



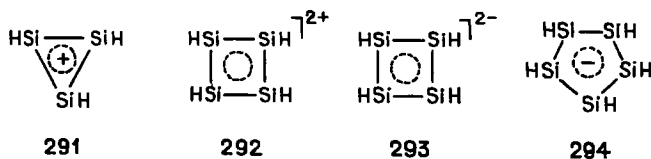
According to *ab initio* calculations of the energies of the homodesmotic (86) and the hyperhomodesmotic (87) reactions (85CC1121), the aromatic stabilization energy of (286) amounts to, respectively, 51 and 48% of that of benzene:



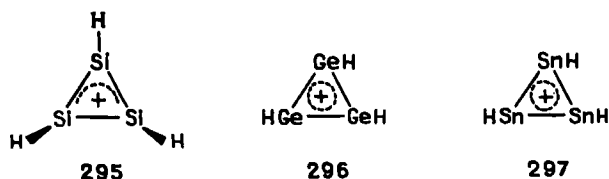
Unlike benzene, the energy of the D_{6h} symmetry structure (286) is only slightly lower (by 3.7 and 0.5 kcal/mol; 6-31G**/3-21G) (85CC1121) than that of the valence isomers (289) and (290) and is even higher than the energy of the hexasilaprismane (288) structure (by 9.5 kcal/mol (85CC1121); 9.9 [86AG(E)651]; 13 kcal/mol, 6-31G**/6-31G* (89CB2121)). Moreover, the structure of hexasilabenzene turned out to be nonplanar. The calculations of eigenvalues of the force constant matrix for (286) (85CC1121; 86JCP1664) carried out with basis sets without inclusion of polarization functions showed that the structure of D_{6h} symmetry corresponded to a minimum on the PES, even though a suspiciously low vibration frequency (b_{2g} mode) was revealed [9 cm⁻¹, DZ (86JCP1664)]. As shown in Nagase *et al.* (87JCP4513), an extension of the basis set and the inclusion of electron correlation led to an essentially different result; namely, the planar structure (286) corresponds to a first-order saddle point, and a chair-type D_{3h} structure (287) with pyramidalized silicon atoms corresponds to a minimum on the PES (as is also the case with the disilene structure) [86CPL(130)115; 87JA4141]. The $D_{6d} \rightarrow D_{3d}$ energy gain is about 1.7 kcal/mol (88MI2). The analogy with disilene is also seen in the triplet instability of the RHF solution for the D_{6h} structure of hexasilabenzene.

As has been shown by a calculation of the temperature evolution of the Gibbs energy differences in the isomeric Si₆H₆ (*g*), at a temperature above 340 K hexasilabenzene (D_{3d} structure) becomes relatively more stable than (288) [89CPL(161)175; 90JST143].

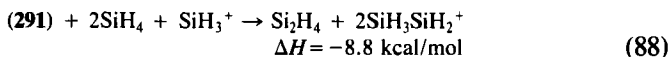
Since the degree of π -aromaticity of annulenes or their ions is inversely proportional to the size of their ring, one should have expected that a more substantial aromatic stabilization would occur in the planar D_{3h} structure of the trisilacyclopentenyl cation (291) (SiH)₃⁺. The MNDO and MINDO/3 calculations (89ZOR196, 89ZSK23) on polysilicon monocyclic ions (283)–(294) that satisfy the $(4n + 2)$ Hückel rule, and on hexasilabenzene (286), have shown that the totally symmetrical planar structures of D_{nh} symmetry with equal lengths of the SiSi bonds, similar to structures of the corresponding hydrocarbon analogs, do not correspond to minima on the



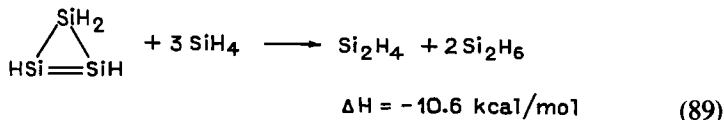
PES, with the exception of structure **(291)**. A cyclic C_{2v} structure **(295)** corresponds to a minimum on the PES of the triplet (3B_2) state; it has an energy 4.5 kcal/mol higher than the D_{3h} structure of the singlet electronic state $^1A'_1$ **(291)**.



According to the MNDO calculations (88MI4), the planar structure of the trigermacyclopentenyl cation **(296)** also corresponds to a minimum on the PES, whereas the analogous structure of $(\text{SnH})_3^+$ **(297)** is a third-order saddle point. The MNDO calculation of the ISE **(291)** [isodesmic reaction (88)], with a correction for the strain energy determined from isodesmic reaction (89), shows the aromatic stabilization of **(291)** to be insignificant (1.8 kcal/mol):

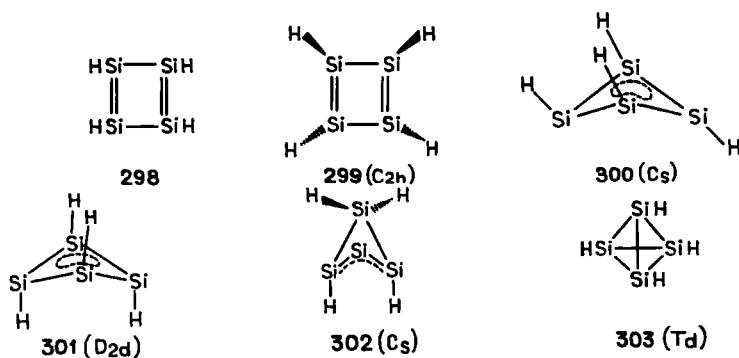


It will be recalled that the structure of the silacyclopentenyl cation **(252)** also does not exhibit aromatic stabilization [83JA(105)4972].



Thus, the insignificant aromatic stabilization cannot, apparently, be a key factor that would determine the stability and structural type of silicon analogs **(286)**, **(291)**–**(294)** of annulene hydrocarbons and their ions. Moreover, this leads to the conclusion that antiaromatic destabilization will not be of importance for the silicon analog of cyclobutadiene, tetrasilacyclobutadiene **(298)**. According to semiempirical MINDO/3 (89MI8) and *ab initio* [86JA4344; 87CC809; 88AG(E)(27)1081, 88CPL(143)421] calculations, the planar D_{2h} structure **(298)** corresponds not to a minimum on the PES, but

rather to a second-order saddle point. The lengths of the bonds Si=Si (2.118 Å) and Si—Si (2.379 Å) in (298) are close to those, calculated with the same set DZ + P for, respectively, disilene (Si=Si, 2.120 Å) and disilane (Si—Si, 2.346 Å) [88CPL(143)421]. The planar structure of symmetry D_{4h} of the lower triplet state $^3A_{2g}$ does not correspond to a minimum on the PES (89ZSK23), in contrast to the analogous structure of cyclobutadiene. The C_{2h} structure of the singlet electronic state with pyramidalized silicon atoms (299), as in disilene (87JA4141), has a lower energy than the planar structure (298) [by 2.4 kcal/mol with MINDO/3 (89ZSK23); by 5.0 kcal/mol (CI-SDQ) (87CC809)]. More stable than (298) or (299) are structures (300) and (301) that correspond to minima on the PES [more stable than, e.g., (298) by 17.5 and 22.0 kcal/mol, respectively (CI)SD(Q)/



DZ + P//DZ + P)] [88CPL(143)421; also see 89MI3]. Note that an analogous structure of cyclobutadiene of D_{2d} symmetry does not correspond to a minimum on the PES (84ZOR886). As has been shown by *ab initio* calculations (89CPL(155)563), the most stable of the structures containing a four-membered Si₄ ring is the C_s structure (302). It has an energy lower by 50.6 kcal/mol than that of tetrasilatetrahedrane (303) (CI-SD(Q)/DZ + P//DZ + P) (89MI3), which also corresponds to a minimum [86JA4344; 87CC809; 88AG(E)(27)1081, 88CPL(143)421, 88MI4; 89ZOR196, 89ZSK23]. The strain energy of (303) is estimated from a calculation of the energy of the homodesmotic reaction, which equals 140.9 kcal/mol (6-31G*) (87CC60). According to MP3/6-31G*//6-31G* calculations (86JA4344), the energy of (303) is 7.4 kcal/mol higher than that of the D_{2h} structure (298).

Thus, with an increase in the number of silicon atoms in a cyclic structure, analysis, in terms of the aromaticity concept, of the structural types and stability loses its prognostic value. A striking example of this is given by the pyramidalization of the Si atoms, typical of disilene, in hexasilaben-

zene and tetrasilacyclobutadiene molecules. The electronic structure and geometric relationships dictated by aromaticity or antiaromaticity also lose their role in going from the silasubstituted to the germa- and stanna-substituted structures. The data given in the Section VI,E warrant the conclusion that the use of the aromaticity concept should be restricted to mono- and disilasubstituted compounds and, possibly, to the monogerma-substituted ones. In the case of these compounds, the deliberate use of the concept provides a rational approach to stabilization of the planar configuration at silicon and germanium centers participating in the formation of multiple bonds $C=X$ and $X=X$ ($X = Si, Ge$).

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